NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

FIVE YEAR STRATEGIC PLAN
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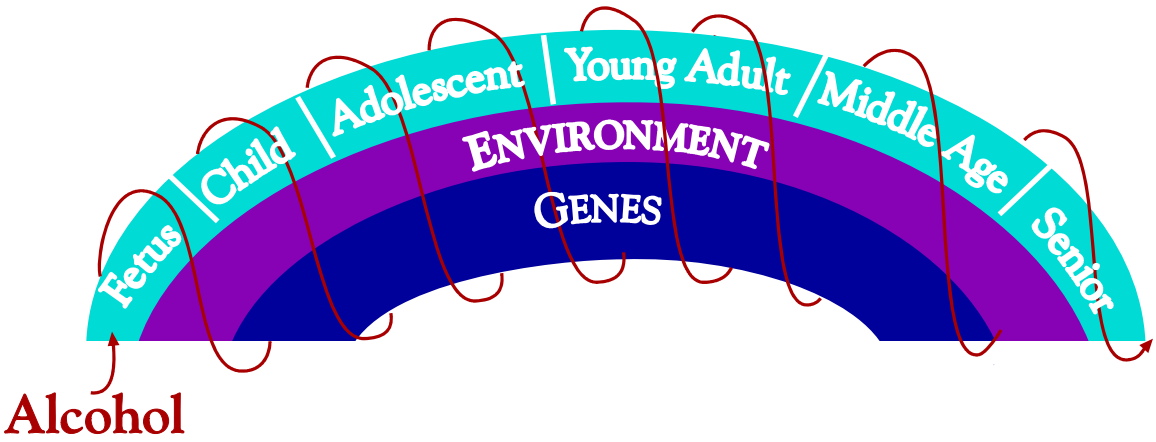

"ALCOHOL ACROSS THE LIFESPAN"

U.S. Department of Health and Human Services
National Institutes of Health
National Institute on Alcohol Abuse and Alcoholism

NIAAA Five Year Strategic Plan
Alcohol Across the Lifespan

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NIAAA FIVE YEAR STRATEGIC PLAN
ALCOHOL ACROSS THE LIFESPAN

EXECUTIVE SUMMARY

Introduction

The National Institute on Alcohol Abuse and Alcoholism (NIAAA), a component of the National Institutes of Health, U.S. Department of Health and Human Services, is the lead agency in this country for research on alcohol abuse, alcoholism, and other health effects of alcohol. This document, the *NIAAA **Strategic Plan** for Research, 2006-2010*, sets forth a new organizing principle for alcohol research studies and describes research opportunities to deepen and broaden our understanding of alcohol use and alcohol use disorders.

Alcohol use disorders (AUD) is defined as alcohol abuse and alcohol dependence, and arise from drinking *too much, too fast and/or too often. Alcohol Abuse* is defined as a recurring pattern of high-risk drinking that creates problems for the drinker, for others, or for society. Adverse consequences can also arise from a single instance of hazardous alcohol use. *Alcohol dependence,* typically considered to be synonymous with *alcoholism* (alcohol addiction), is a complex disease characterized by persistent and intense alcohol-seeking, which results in a loss of control over drinking, a preoccupation with drinking, compulsion to drink or inability to stop, and the development of tolerance and dependence.

The U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) recently came to similar conclusions about the toll taken by excessive alcohol use. According to the CDC, excessive alcohol consumption is the number-three cause of preventable death in the United States. The WHO also ranks alcohol third among preventable risk factors for premature death in developed nations. In 2003, the worldwide prevalence of alcohol use disorders (AUD) was estimated at 1.7%, accounting for 1.4% of the total world disease burden in developed countries. In the United States, 18 million Americans (8.5% of the population age 18 and older) suffer from alcohol use disorders. Only 7.1% of these individuals received any treatment for their AUD in the past year. Problems related to the excessive consumption of alcohol cost U.S. society an estimated $185 billion annually.

In addition to the adverse health effects that result directly from excessive alcohol consumption, other medical conditions often co-occur among individuals with excessive alcohol consumption. For example, alcohol abuse and dependence commonly occur in people who abuse other drugs, and in people with mood, anxiety, and personality disorders. An estimated 90% of cocaine addicts have alcohol problems and as many as 60% of patients at community mental health centers have alcohol and other drug abuse disorders. The high co-occurrence of alcohol and tobacco dependence poses special problems. An estimated 50% to 90% of alcohol dependent individuals are smokers who, in general, smoke heavily, become more addicted to nicotine and are less successful at quitting smoking than other smokers. This puts them at a much higher risk for certain cancers and cardiovascular diseases that develop more readily in the presence of both alcohol and nicotine.

Lifespan Perspective

Investigators traditionally have pursued solutions to the wide range of alcohol-related issues through studies of alcohol's effects on biological systems, the genetic factors underlying these biological effects, and the environmental and cultural factors that influence alcohol use. This Plan applies a new organizing principle – the lifespan perspective – to these diverse areas of alcohol research. Scientists now recognize that human biology and behavior continues to change throughout life and changes occurring throughout the lifespan affect individuals' drinking patterns as well as the decisions they may make to change their drinking habits or to seek help for alcohol use problems. A lifespan perspective will allow researchers to identify how the emergence and progression of drinking behavior is influenced by changes in biology, psychology, and in exposure to social and environmental inputs over a person's lifetime, and vice versa. This approach should help researchers discover life stage- appropriate strategies for identifying, treating, and preventing alcohol use disorders.

Contributions to Alcohol Use and Alcohol Problems Across the Lifespan

Numerous factors influence the onset and continuation of alcohol use by an individual. The factors include the individual's genetic makeup, the environments to which he or she is exposed and complex ways that genes interact with one another and with the environment. These same factors determine an individual's pattern of alcohol consumption and the risks for developing alcohol dependence (alcoholism).

Some of the first evidence of the importance of the lifespan perspective for understanding alcohol use disorders emerged less than ten years ago in an analysis of data derived from NIAAA's National Longitudinal Alcohol Epidemiologic Study (NLAES). This analysis revealed that people who begin drinking at young ages have a significantly increased risk for developing alcoholism. This finding was confirmed by the recent National Epidemiologic Survey on Alcohol-Related Conditions (NESARC), which showed that young people who began drinking before age 15 are four times more likely to develop alcohol dependence during their lifetime than those who began drinking at age 21. This is true for individuals from families where a parent had a history of alcoholism and for individuals with no parental history of alcoholism. Therefore, while parental history clearly contributes to the risk for developing alcoholism, likely a reflection of genetic risk factors, early initiation of drinking is also an important predictor of risk for alcoholism. Researchers hypothesize that early exposure to alcohol may alter brain development in ways that increase an individual's vulnerability to alcohol dependence. Some other biological factor, perhaps affecting personality, may also be responsible for both the early onset of drinking and the heightened risk for alcoholism.

Alcohol Policy and Public Health

A wide range of alcohol policies may affect alcohol consumption and other behaviors relating to alcohol, and can have important influences on public health outcomes. In the United States, laws, regulations, and jurisprudence address various aspects of alcohol use ranging from alcohol taxation to behaviors affected by alcohol, such as drinking and driving. Scientific research has identified a number of alcohol-related policies that have significant effects on public health outcomes. Examples of these include a reduction in the number of traffic fatalities (raising the minimum drinking

age to 21, enforcing stricter drinking and driving penalties), a reduction in child abuse and sexually transmitted diseases (raising taxes on alcohol beverages), and enhancement of access to alcohol treatment programs (State-mandated provision in health care financing). In general, alcohol policies are designed to serve individuals at all levels of the lifespan through harm reduction and prevention of alcohol-related illness or injury.

Lifespan Perspective – Practical Implications

Understanding the interactions of alcohol with stages of life will enable us to address the prevention and treatment of alcohol problems in a life stage-appropriate manner. In particular, such an approach should lead to a better understanding of:

• how alcohol perturbs development of the embryo and fetus, which may help reduce the impact of Fetal Alcohol Spectrum Disorders (FASD).

• how genetic and environmental factors contribute to drinking initiation and the development of alcohol dependence, which will foster the rational design of prevention strategies that target specific risk factors at appropriate stages of the lifespan.

• the factors that influence the common phenomenon of naturally “aging out” of alcohol dependence, to aid in the development of new therapeutic approaches and to help achieve behavioral change in alcoholism treatment.

• how alcohol use produces functional and structural changes in the nervous system, which will aid in the development of behavioral and pharmacological therapies directed to specific molecular targets within the brain.

• how the products of alcohol metabolism contribute to the development of alcohol-induced diseases of the liver, digestive system, lung, heart, brain, endocrine and immune system. Such knowledge could help develop better preventions and treatments for these disorders.

RESEARCH OPPORTUNTIES AND OUTREACH

The following is a brief outline of Research Opportunities and Outreach activities identified by NIAAA that will help guide the Institute's research program and activities over the next 5 years.

Opportunities that Transcend the Lifespan Perspective

Several scientific issues have impact on all stages of life. While the manner by which they affect an individual may differ depending upon the person's stage of life, these issues are best considered from an overarching perspective and include: alcohol metabolism; genetic and environmental influences including epigenetics; neurobiological effects of alcohol; and improvements in the diagnostic recognition of alcohol use disorder.

Metabolism -- Individuals differ in how fast they metabolize alcohol and in the extent to which they are affected by a given dose of alcohol. These differences affect drinking behavior, the potential for the development of alcohol dependence, and the risk for developing alcohol-induced organ damage.

- Enhance understanding of the differences in alcohol *pharmacokinetic*s (the rate by which an individual metabolizes alcohol) and *pharmacodynamics* (the extent to which an individual is affected by a given dose of alcohol) in their respective contributions to alcohol dependence and organ pathologies arising from alcohol use.

- Continue to identify pathways through which alcohol is metabolized, as well as the effects of alcohol and its two main metabolic products, acetaldehyde and acetate, in altering key metabolic events in the body. Emerging metabolomics technologies can be applied to this effort.

- Identify unique alcohol metabolites and investigate their involvement in pathologic processes, including the development of AUDs.

- Identify metabolic profiles that provide an early indication of alcohol use disorders and alcohol-derived pathologic diseases.

- Continue to investigate how alcohol alters the oxidative state of the cell, the pathologic consequences of the changes in oxidative state, and mechanisms by which alcohol alters the cellular defenses against oxidative damage.

Alcohol and Gene/Environmental Interactions -- Neither genes nor environment alone can explain why any particular individual develops alcohol dependence. Rather, as a complex disorder, risk for alcohol dependence is a consequence of the interplay of multiple genes, multiple environmental factors, and the interaction of these genes and environmental factors. The alcohol field has benefited from the ability to model various aspects of alcohol consumption in animal models, but advances in our understanding of neurobehavioral aspects of drinking and its consequences requires the development of new models. The identification of a number of genes contributing to the vulnerability to alcohol dependence in human

studies, coupled with technological advances including the ability to conduct genome-wide association studies, offer great promise to further define genetic risk factors and their interactions with environmental factors.

- Develop new animal models that more closely resemble diverse human traits regarding alcohol use, to aid the study of alcohol dependence and pharmacotherapy development.

- Continue to identify genes associated with vulnerability for alcohol dependence by employing new and emerging technologies, particularly on samples from study populations previously recruited for genetic research on alcohol dependence (e.g., the Collaborative Study on the Genetics of Alcoholism).

- Identify, through the study of discordant twin pairs, the relative influence of gene and environment on the risk of developing alcohol dependence or abuse.

- Work to incorporate alcohol-related measures, including alcohol use disorders, family history of alcoholism, and detailed measures of alcohol consumption, into the National Health and Nutrition Examination Survey (NHANES) so future efforts can be undertaken to study the effects of interactions between alcohol-related measures and environmental factors such as diet, physical activity, smoking, and exposure to toxins, on risk factors for chronic disease.

Epigenetics -- Metabolic and environmental factors can influence the manner in which genes are expressed through a process known as epigenetics. Epigenetics refers to stable alterations in the genome, sometimes heritable through cell division, that do not involve the DNA sequence itself. Epigenetic processes act as an additional source of biologic variation beyond that attributable to the genetic code. These processes involve the chemical modification of the constituents of the chromosome, the DNA molecules and the gene-regulating proteins known as histones, and may occur as a consequence of exposures to specific environmental substances and stimuli.

- Explore how alcohol alters normal processes associated with chemical modification of DNA and histone proteins, and the consequences of these modifications on gene expression. In addition to epigenetics, identify other mechanisms (e.g., alterations in transcription factors, small inhibitory RNA, etc.) by which alcohol may act to alter gene expression.

- Examine epigenetic effects of alcohol across the lifespan, including alterations in embryonic and fetal development, adolescent and young adult brain maturation, the development of alcohol dependence and organ disease, and potential changes occurring in the later years of life.

Neurobiology -- The brain, which is the primary target for alcohol-induced neurotoxic effects including alcohol dependence, continues to develop and mature from conception through birth into early adulthood. Alcohol consumption may affect

the normal physiology of the central nervous system at any point throughout the lifespan, and those effects may differ depending on lifespan stage.

- Define the full range of *pharmacodynamic* effects of alcohol on central nervous system function and the variability associated with unique genetic and gene-environment profiles.

- Continue to investigate how changes in brain structure and function arise from alcohol use. Such studies could include using the newest imaging technologies, diffusion tensor imaging MRI (dtMRI), for example, to study alcohol-induced changes in white matter tracts in the brain.

- Apply new techniques for quantifying neurotransmitters, receptors and transporters to obtain a more complete understanding of alcohol's effects on these systems.

Diagnosis of Alcohol Use Disorders -- While the diagnostic criteria for alcohol dependence and alcohol abuse provided in current diagnostic schemes, including the DSM-IV and ICD-10, have contributed to improved case recognition and served researchers well over the past decade, research has begun to focus on developing quantitative representations of these criteria using statistical methods that provide differential severity weighting for individual AUD symptoms and allow for the inclusion of alcohol consumption variables. The development of quantitative criteria will lead to better understanding of the pathological stage of the disease for any given individual, provide the researcher an improved understanding of the etiology of alcohol dependence, and augment translational research to develop improved treatment approaches for the differing severity levels of alcohol dependence.

- Pursue the development and assessment of dimensional or quantitative criteria as an improved indicator of alcohol use disorders, for both categorization and severity determination.

- Develop biomarkers for chronic alcohol use, for example through the exploration of alcohol on glycoproteomics and lipidomics.

- Determine if expression of AUDs differs by age, sex, and race-ethnicity variables and establish criteria for identifying AUDs that takes such differences into consideration.

Opportunities: Embryo and Fetus

The earliest stages of life are periods of great vulnerability to the adverse effects of alcohol. Embryonic and fetal development are characterized by rapid, but well-synchronized patterns of gene expression, including epigenetic imprinting, which makes the embryo/fetus particularly vulnerable to harm from alcohol, a known teratogen (an agent capable of causing physical birth defects). Alcohol's teratogenic effects were recognized over three decades ago, and it is now the leading known environmental teratogen. Alcohol may also damage neurological and behavioral development even in the absence of obvious physical birth defects. Alcohol-induced birth defects are known

as fetal alcohol spectrum disorders (FASD). The severity of defects depends on the dose, pattern, and timing of *in utero* exposure to alcohol. Research in animal models has demonstrated that the potential for adverse effects increases with the maternal blood alcohol concentration (BAC). Research has also suggested that alcohol's causative role in FASD can be influenced by maternal hormones, nutrition, age, parity, years of drinking, and genetic factors. The most serious adverse consequence of prenatal alcohol exposure is *fetal alcohol syndrome* (FAS), a devastating developmental disorder characterized by craniofacial abnormalities, growth retardation, and nervous system impairments that may include mental retardation. Children and adults with FAS have irreversible neurobiological deficits that affect multiple systems, ranging from motor control to executive function.

- Apply genetic and proteomic technologies to examine alcohol's effects on gene expression patterns involved in normal development.

- Identify alcohol's role in epigenetic modifications of DNA and histone structure.

- Examine the interaction of alcohol with additional factors, such as maternal stress and nutritional stress, in altering epigenetic patterns, and identify the sites where the interaction of these factors changes the genetic expression pattern.

- Identify the mechanisms through which alcohol impairs the functioning of various neurotransmitter systems, second messenger signaling systems, and cell adhesion communication systems.

- Use knowledge gained in uncovering target sites for alcohol's action on the embryonic and fetal stages of life to begin developing potential therapeutic or preventative interventions, including dietary supplements (e.g., antioxidants and choline) that are safe for use in pregnant women.

- Apply metabolomics technology to the search for a metabolic profile that may serve as a marker for risk or vulnerability for FASD.

- Use computer technologies for the analysis of 3-D facial images and MRI brain scans to identify changes in FASD and other disorders of children to refine the understanding of the neurodevelopmental signature of FAS and FASD.

- Refine and increase knowledge about specific structural alterations in various brain regions for identifying fetal alcohol CNS deficits, and explore the potential for developing low-cost or modest-cost approaches for identifying these structural deficits through prenatal ultrasound and transfontanelle ultrasound of newborns.

- Identify barriers to implementing alcohol screening in primary care and obstetric practice, and explore the acceptability of new screening technologies, such as computer assisted interviewing.

- Continue to develop and refine approaches for selected and indicated prevention, to decrease the potential for FASD births among the women at greatest risk for these disorders.

Outreach: Embryo and Fetus

- NIAAA will continue to support the meetings and work of the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFAS), which is developing a strategic plan with actions that involve the participation of alcohol researchers and research administrators. NIAAA and other ICCFAS agencies will co-sponsor Research to Practice Meetings on diverse FASD issues. NIAAA will continue to work with the Substance Abuse and Mental Health Services Administration (SAMHSA) on the development of guidelines and training materials for criminal justice personnel.

- NIAAA will partner with the Health Resources and Services Administration (HRSA) and the National Organization on Fetal Alcohol Syndrome (NOFAS) in an effort to include alcohol screening in maternal care programs and beyond and to identify research-based interventions that can be implemented in a cost effective manner in health care facilities.

- NIAAA will co-sponsor, with NICHD, NCI, and NCCAM, an initiative for a multi-center international research network designed to conduct randomized clinical trials of interventions to reduce the major risks to maternal, neonatal, infant and early childhood health in resource-poor countries. NIAAA seeks to include alcohol screening and interventions in the health care of women in prenatal care and the screening of children from birth through early childhood for the disabilities that result from prenatal exposure to alcohol.

Opportunities: Early and Middle Childhood

- Apply the various collection stategies with stafe of the art tecnologies in genomics, imaging and statistical modeling to determine the relative contribution of biology, environment, and genetics to risk for alcohol dependence or abusive alcohol consumption in later life.

Opportunities: Youth and Adolescence

The beginning of adolescence is demarcated biologically with the onset of puberty, and is understood to end when an individual assumes adult roles and responsibilities. Puberty consists of many biological processes that do not occur at the same chronological age and do not necessarily progress at the same pace or have the same pattern of unfolding in every individual. Importantly, brain development, marked by continuous generation of neurons and connections between neurons, and the refinement of communication among those neurons, continues during puberty and into the young adult ages. Drinking alcohol during this dynamic period of brain development may result in brain effects leading to an earlier onset of alcohol-induced specific diseases or to an earlier transition towards the development of alcohol use disorders. Very important to understanding alcohol use by youth from a developmental perspective is the fact that, over the past 100 years, the endocrine changes associated with puberty have been occurring at younger ages, while the attainment of adult roles such as starting a career, finding a partner, owning a home and becoming a parent are occurring much later. The result is the dramatic expansion of the period referred to as adolescence which prolongs the potential duration of one of the heaviest drinking periods of the lifespan and therefore may exacerbate the harmful effects on alcohol on development. In sum, adolescence is a period of dramatic biological change – occurring in the context

of equally dynamic socio-environmental change with regard to the adolescent's school, peer group, family, and social milieu. The majority (80%) of youth begin to drink by the end of high school, and some experience significant alcohol-related problems including the development of alcohol use disorders.

- Identify alcohol's effects on developing brain structures and behavioral regulatory systems.

- Use specific modifications in imaging techniques to visualize changes associated with white matter tracts, and correlate changes in brain structure and function with neuropsychological functioning.

- Expand studies on the adolescent decision-making process, including the influence of affect, external environmental factors, and expectations on those decisions. Use laboratory simulated environments as well as animal research, particularly in primates.

- Refine definitions of alcohol abuse and dependence currently used for adults to apply to youth and adolescents for better diagnosis of and screening for adolescent alcohol problems.

- Identify alcohol behavioral markers for problem alcohol use by youth, especially for very early markers of risky drinking.

- Identify the relationship among reproductive hormones, stress hormones, and sex differences in alcohol use and dependence that unfolds during late puberty, through longitudinal studies of hormonal, electrophysiological and other biological factors over the course of puberty.

Outreach: Youth/Adolescence

- NIAAA recently published a monograph devoted to underage drinking and development entitled, "Alcohol Development in Youth, A Multidisciplinary Overview" (Alcohol Research and Health, Vol. 28, Number 3, 2004/2005). This monograph covered a wide range of topics as reviewed by NIAAA staff members and extramural research investigators serving on the Underage Steering Committee.

- NIAAA will develop a working relationship with the Department of Agriculture's 4-H and other youth programs to determine how these programs might be included in efforts to reduce underage drinking. The outcomes of pilot projects and activities will be evaluated to determine effectiveness.

- Use state-of-the-art communication strategies and techniques to increase awareness of critical alcohol and health messages, including – "Early onset of alcohol use interacts with human developmental processes to increase risk for alcohol problems throughout the lifespan."

- NIAAA participates in a joint *Social Neuroscience* RFA with NIDA and NIA at NIH, and the Institute of Neurosciences, Mental Health and Addiction in

Canada. The purpose of this initiative is to stimulate research on the brain mechanisms underlying social behaviors, including social decision making, interpersonal/peer relationships, self-regulation, and emotional regulation as they relate to the development of adolescent alcohol abuse and dependence.

Opportunities: Young Adult

Entry into young adulthood is defined by a variety of self-directed transitions that signal an individual's burgeoning independence from parental care. The pursuit of post-secondary education, enlisting in the military, and entering the workforce are a few such milestones, which traditionally have occurred when an individual is in his or her late teens or early twenties. Other events that traditionally mark this period include assuming large financial obligations, courtship, and marriage. In the U.S, most states have adopted age 18 as the legal age of majority – the point at which individuals assume responsibility for their own actions. However, from a developmental rather than a legal perspective, emerging or young adulthood now comprises an extended period of unsettled behavior for many individuals, as age of marriage and age of career initiation in the U.S., for example, have increased relative to historic norms. Compared to all other age groups, the prevalence of periodic heavy or high-risk drinking is greatest among young adults aged 18 to 24. Alcohol use disorders including alcohol dependence (alcoholism), also peak during this period. While most young adults transition out of harmful drinking behaviors, a minority will continue to drink heavily into the later stages of adulthood. These phenomena raise important research questions. For example, what factors allow some young adults to discontinue harmful drinking patterns, most often in the absence of formal alcoholism treatment? Why do others experience protracted alcohol problems well into their adulthood?

- Examine the population of non-college and non-military bound young adults as they transition from high school into adulthood, as these individuals are not exposed to post-secondary educational information regarding the consequences of alcohol misuse, nor are they in a structured environment that encourages brief interventions or treatments.

- Apply new technologies in neuroscience research to improve understanding of how changes in the young adult brain influence early onset drinking, with respect to the neural connections underlying the decision making process, and to alcohol-induced injury in brain versus other organs in young adults.

Outreach: Young Adult

- Audience segmentation research conducted at NIAAA has revealed binge drinking young urban adults to be a well-delineated group of individuals at significant risk for alcohol-related problems. We have rich descriptive data about the lives and habits of binge drinking in this population, which can provide a strong and unique foundation for programmatic prevention intervention research for these at-risk young adults.

- NIAAA has collaborated with the Office of Juvenile Justice and Delinquency Prevention (OJJDP) in evaluating its initiative to address underage drinking in

rural communities and plans to work with OJJDP and the Air Force to evaluate an Air Force Base –Community Partnership to reduce drinking among servicemen under age 21. NHTSA continues to participate in the NIAAA programs to reduce underage drinking in college students. Opportunities exist to increase interactions and partnerships with the Department of Defense agencies involving collaborations with OJJDP and NHTSA.

- NIAAA has attempted to include underrepresented Asian Americans and Pacific Islanders as researchers and as study participants. An ongoing collaborative alcohol research planning grant at the University of Hawaii is one example of NIAAA efforts in this regard. NIAAA also is working with the National Association of Asian and Pacific Island Families Against Substance Abuse (NAPAFASA) to develop culturally and language-appropriate information on alcohol use and abuse and health.

- NIAAA will explore opportunities to work with a new CDC Center of Excellence in Health Marketing and Health Communications at the University of Connecticut. The University of Connecticut Center includes efforts to reduce drug and alcohol use among youth and young adults.

- NIAAA will update/re-issue college drinking report in 2007.

- NIAAA will use college drinking process/materials as a template for developing and disseminating essential alcohol messages and materials for the gamut of lifespan stages.

Opportunities: Midlife

A broad spectrum of alcohol-related problems and issues becomes manifested during the adult period of life often referred to as midlife. At midlife, many of the pathological consequences of heavy alcohol use become most evident, and individuals with alcohol dependence are most likely to seek treatment of their alcoholism at this time.

Metabolism and Organ Injury

- Identify the differing metabolic fates of alcohol, the extent to which alcohol metabolism alters other metabolites and the oxidative state of the cell, and the consequences of these perturbations on organ function and disease.

- Investigate how alcohol influences the disease course of various pathogens, such as Hepatitis C and Hepatitis B.

- Identify the effects of alcohol at low and moderate dose levels to uncover the mechanism underlying both pathologic and potential beneficial outcomes of alcohol exposure at these levels.

- Examine whether alcohol's effect on HIV infection and AIDS progression varies with age of infection

- Identify the alcohol-related factors associated with increased HIV infectivity, such as viral shedding, the alteration of HIV variants through such processes as epigenetics, and the potential effect of alcohol on metabolism of anti-HIV medications.

- Determine the implications of alcohol and AIDS basic science discoveries for prevention and treatment research.

Treatment and Behavioral Change

- Identify biological factors and contextual social factors that contribute to the decisional process to change drinking behavior as part of the transitional process from alcohol dependence to recovery, and the factors underlying sustained recovery among those individuals who succeed in both the presence and absence of professional treatment.

- Increase understanding of the role of social context (marital or other partners, friendship and kin networks, employment environments, legal and economic environment, e.g.) in promoting or retarding positive change in drinking behavior.

- Apply new technologies in neuroscience research to understand how acute as well as chronic alcohol use affects neural circuits and how neural circuits are modified by treatment and recovery.

- Apply insights and methods developed in neuroscience, immunology, oncology, sociology, genomics, metabolomics and other fields to study change in drinking behavior.

Medications Development

- Identify new target sites in the brain for which lead compounds could be developed.

- Develop animal models that more closely reflect the human endo- and intermediate phenotype underlying the clinical syndrome phenotype.

- Develop paradigms that model surrogate outcomes for alcoholism treatment using human laboratory paradigms.

- Identify characteristics of patients that predict efficacy and safety of different medications using pharmacogenetic research approaches.

- Continue research targeted to the prevention and treatment of alcohol-related organ pathologies involving anti-oxidant agents, and cannabinoid-related agents.

- Develop collaborative networks among government, academia, and industry to overcome the challenges in development of medications to treat alcohol problems.

Outreach: Midlife

- NIAAA has working relationships with many organizations whose missions and goals are to help move research results to practice and to the public. The NIAAA collaborates with these organizations in symposia, workshops and meetings and provides support in the distribution of alcohol research knowledge.

- NIAAA partners with the School of Medicine at Howard University to mentor pre-doctoral students in research, seminars, examinations and short-term rotations. This partnership allows NIAAA: to explore mechanisms and develop hypotheses for alleviating health disparities in alcohol related problems; provide education and information to the community and to health care providers; increase the participation of minorities in research studies at NIAAA and Howard University.

- Use state-of-the-art communication strategies and techniques to increase awareness of critical alcohol and health messages, including that: research-based treatments improve the health and well-being of individuals with alcohol problems; research promises to further elucidate mechanisms of alcohol damage and lead to targeted interventions.

Opportunities: Senior Adult

Aging is associated with a variety of changes that place senior adults at special risk for alcohol-related health problems. Senior adults are known to differ in their physiological and behavioral responses to alcohol in a variety of social contexts, and their ability to develop tolerance to alcohol is greatly altered during the senior years. Drinking can aggravate a variety of pathological conditions in the senior adult including stroke, hypertension, neurodegeneration, memory loss, mood disorders, and cognitive or emotional dysfunction. As the percentage of persons in the senior age category is rapidly growing in the United States, improving knowledge about the effects of alcohol at this life stage is becoming increasingly important.

- Use current technologies of genomics, proteomics, and metabolomics to achieve a more detailed understanding of alcohol metabolic pharmacokinetics in senior adults.

- Focus on the effectiveness of emerging medications used to treat AUDs in the senior adult population, given the nature of potential drug interactions with medications typically prescribed in this specific population.

- Through collaborative efforts across the NIH, conduct longitudinal research to assess the use, impact, and consequences of alcohol upon the aging population and the development of such disorders as Alzheimer's disease, Type II diabetes, and other health problems that increase with age.

- Through animal models of aging and alcohol use, examine the specific contributions of alcohol to aging organ pathology (e.g., brain, liver, pancreas, heart).

Outreach: Senior Adult

- Working with the NIA, Association for the Advancement of Retired Persons (AARP) and Medicare, NIAAA will increase the transfer of information to practice for seniors through publications and assuring that health care providers have appropriate information. Co-sponsorship of meetings and conferences will be used to foster working relationships.

CHAPTER I. OVERVIEW

The National Institute on Alcohol Abuse and Alcoholism (NIAAA), a component of the National Institutes of Health, U.S. Department of Health and Human Services, is the lead agency for U.S. research on alcohol abuse, alcoholism, and other health effects of alcohol. Its role is enunciated in the Institute Mission Statement:

A. Mission and Vision of NIAAA

The **NIAAA Mission** is to provide leadership in the national effort to reduce alcohol-related problems by:

- Conducting and supporting research in a wide range of scientific areas including genetics, neuroscience, epidemiology, health risks and benefits of alcohol consumption, prevention, and treatment
- Coordinating and collaborating with other research institutes and Federal Programs on alcohol-related issues
- Collaborating with international, national, state, and local institutions, organizations, agencies, and programs engaged in alcohol-related work
- Translating and disseminating research findings to health care providers, researchers, policymakers, and the public

The Institute's efforts to fulfill its mission are guided by the **NIAAA Vision** to support and promote, through research and education, the best science on alcohol and health for the benefit of all by:

- Increasing the understanding of normal and abnormal biological functions and behavior relating to alcohol use
- Improving the diagnosis, prevention, and treatment of alcohol use disorders
- Enhancing quality health care

This document, the *NIAAA **Strategic Plan** for Research, 2006-2010*, sets forth research opportunities to increase our understanding of why, how, and when people drink, why and how some people develop alcohol use disorders (AUD). Throughout the years, investigators have pursued answers to these very questions through studies of alcohol's effects on biological systems, the genetic factors underlying biology, and through the study of environmental and cultural factors. This Plan, however, adds a new direction to alcohol studies by applying the lifespan perspective -- the consideration of how the emergence and progression of drinking behavior is influenced by multiple changes (in biology, psychology, and in exposure to social and environmental inputs) over a person's lifetime. These changes occurring throughout the lifespan affect the pattern of drinking (quantity and frequency) and the actions individuals may take to modify their drinking behavior or to seek help for an alcohol-use disorder. Viewing alcohol use and alcohol problems through a lifespan perspective will provide knowledge that will, through early identification and intervention, significantly contribute to the ability to decrease the prevalence of alcoholism and other alcohol-related disorders, and to the treatment of these disorders.

This overview describes the origins of the lifespan perspective, highlights the complexity of alcohol issues in health, and provides a view to why solutions to these

problems cannot be approached from any single discipline but must be approached in a multidisciplinary and transdisciplinary manner. Further, the findings at any investigative level (molecular, cellular, animal model, human laboratory, human clinical to community) must be translated to other levels and eventually to clinical practice in the world environment. Transdisciplinary and translational research over the course of the next decade will be aided by the intellectual and technical developments arising from the NIH Roadmap and the NIH Neuroscience Blueprint, and their potential application to address health issues related to alcohol use has been integrated into this Plan.

B. Drinking Patterns and their Definitions

An understanding of the drinking patterns that exist in the population, as well as the alcohol-use disorders that arise from drinking *too much, too fast and/or too often,* is important for identifying targets for future research pursuits.

Alcohol Abuse and *Alcohol Dependence* are two clinical disorders characterized by either a persistent pattern of inappropriate alcohol use or of adverse consequences. *Alcohol dependence* is typically considered to be synonymous with *alcoholism*. *Alcohol abuse* and *alcohol dependence* may be defined as shown in Tables I-1 and I-2. A proposal has recently been made to use the term addiction to specify the behavioral, CNS neuroadaptive responses to chronic alcohol exposure vis a vis loss of control, preoccupation with drinking and compulsion to drink, as distinct from the physiological dependence symptoms of tolerance and withdrawal.

Table I-1. Definition of Alcohol Abuse

A recurring pattern of high-risk drinking that results in adverse outcomes, including:

- ***** Personal problems: memory and cognition; job, family, friends, and other significant relationships; health and organ damage
- ***** Problems to others: injury and death; violence and crime (property damage, assault, homicide)
- ***** Problems for society: underage drinking; health care costs; economic productivity
- ***** Use in hazardous situations

Table I-2. Definition of Alcohol Dependence (Alcoholism)

A complex disease characterized by a persistent and progressive pattern of abnormally intense alcohol-seeking behavior that, over time, results in:

- * loss of control over drinking
- * a preoccupation with drinking
- * compulsion to drink/unable to stop
- * the development of tolerance and dependence

While alcohol abuse and alcohol dependence reflect harmful drinking that are either recurrent or persistent, adverse consequences from alcohol use can arise among individuals who may have used alcohol in a hazardous manner to excess on only one occasion. These adverse consequences include alcohol-related traffic crashes, drownings, and alcohol poisonings, among many others.

Drinking in a manner that will cause intoxication clearly poses risks to the drinker. A term frequently used to describe this pattern is *binge drinking.* Different definitions often have been used for this pattern of drinking. To provide clarification, the National Advisory Council on Alcohol Abuse and Alcoholism (NAC) in 2004 developed a standard definition for *binge* drinking as a pattern of drinking alcohol that brings the blood alcohol concentration to 0.08 gram percent (the legal limit for drinking and driving in all states) or above. The NAC further noted that for a typical adult male, this BAC level may be obtained after the consumption of 5 drinks in a 2 hour period, and for females, 4 drinks in the same period. The Council definition of binge drinking and recommendations are provided in Table I-3.

Table I-3. Definition of Binge Drinking

A "binge" is a pattern of drinking alcohol that brings blood alcohol concentration (BAC) to 0.08 gram percent or above. For the typical adult, this pattern corresponds to consuming 5 or more drinks (male), or 4 or more drinks (female), in about 2 hours. Binge drinking is clearly dangerous for the drinker and for society.

* In the above definition, a "drink" refers to one serving of 12 g of absolute alcohol (e.g., one 12-oz. Beer, one 5-oz. glass of Wine, or one 1.5-oz. Shot of distilled spirits).
* Binge drinking is distinct from "risky" drinking (reaching a peak BAC between .05 gram percent and .08 gram percent) and a "bender" (2 or more days of sustained heavy drinking).
* For some individuals (e.g., older people or people taking other drugs or certain medications), the number of drinks needed to reach a binge level BAC is lower than for the "typical adult".
* People with risk factors for the development of alcoholism have increased risk with any level of alcohol consumption, even that below a "risky" level.
* For pregnant women, any drinking presents risk to the fetus.
* Drinking by persons under the age of 21 is illegal.

Source: NIAAA, National Advisory Council, February, 2004

Binge drinking is common across most life stages. Fifty percent of college students who drink engage in binge drinking, and twenty percent do so twice or more every three weeks. More than two-thirds of binge drinking episodes in the U.S. occur among adults age 26 and older, and half of all binge drinking episodes occur among people who otherwise drink moderately.

The NIAAA also provided a definition of moderate drinking as this term has been used in many different ways. Moderate drinking is defined by the NIAAA as consuming up to two drinks per day for men and one drink per day for either women or older adults. While moderate drinking is considered to offer some benefits to some individuals, drinking at this level poses real risks for others. For example, women who are pregnant or considering pregnancy, persons driving or operating heavy machinery, and those taking one or more of the more than 150 medications that interact with alcohol should not drink even moderately. Persons with a high vulnerability to develop alcohol dependence may be encouraged to refrain from alcohol use.

The National Epidemiological Survey on Alcohol and Related Conditions (NESARC) study completed its first wave of data collection, which involved recording the responses to questions posed to over 43,000 individuals about alcohol and other drug use, abuse and dependence, and their associated disabilities. These data were used to develop extremely valuable information relating quantity and frequency of alcohol use to the risk of developing alcohol abuse and alcoholism. These data have been used to establish the following cut points for *risk drinking*, which mirrors the definition for moderate drinking*:* Exceeding 2 drinks per day for men, 1 drink for women, and 14 drinks per week for men and 7 drinks per week for women. The NESARC data revealed that, compared with individuals who adhere to the weekly and daily limits, those who exceed only the weekly limits have an 8-fold increase in risk for developing alcohol abuse and a 12-fold increase in risk for becoming alcohol dependent at some point in their lives (Table I-4). Exceeding daily limits once a week or more increases risk for alcohol abuse by 30-fold, and for dependence by 80-fold. Exceeding both weekly and daily limits increases the risk of alcohol dependence by more than 200-fold.

Table I-4. U.S. Adult Drinking Patterns and Risks 2001-2002: Odds Ratios

Alcohol screening limits – number of drinks: In a typical WEEK—14 (men), 7 (women) On any DAY—4 (men), 3 (women)		*An Individual's Odds of Having An Alcohol Disorder Are Increased by a Factor of:*	
DRINKING PATTERN	**Percent of U.S. adults aged 18+**	**Abuse** *without dependence*	**Dependence** *with or without abuse*
Never exceeds the weekly or daily screening limits	**72%**	**Reference Group (1.0)**	**Reference Group (1.0)**
Exceeds only the weekly limits	**2%**	**7.8**	**12.4**
Exceeds only the daily limit less than once a week	**14%**	**17.0**	**33.0**
Exceeds only the daily limit once a week or more	**2%**	**31.1**	**82.0**
Exceeds both weekly and daily limits once a week or more	**10%**	**31.1**	**219.4**

Source: NIAAA 2001-2002 NESARC data

C. Prevalence of Alcohol Problems and Their Consequences

How extensive are the health problems arising from inappropriate alcohol use and what are those problems? Excessive, long-term alcohol consumption can cause a

variety of adverse health effects, including alcoholic liver disease, alcoholic pancreatitis, brain damage, and cardiomyopathy and compromised immune and endocrine functions. Excessive drinking is also associated with an increased risk for cancers of the esophagus, liver, and larynx, irregular heartbeats, and can exacerbate the health consequences of infection with hepatitis C, HIV and other infectious agents. Alcohol consumption can also alter neuronal function, resulting in cognitive deficits, and in neuroadaptations that contribute to the behavioral changes observed with alcoholism (tolerance, sensitization, loss of control, dependence, withdrawal, and relapse).

Epidemiologic data inform us of the problems associated with alcohol consumption and, when collected over time, allow us to track our progress in addressing these problems. The U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) recently came to similar conclusions about the toll taken by alcohol misuse. According to the CDC, excessive alcohol consumption is the number-three cause of preventable death in the United States. The WHO also ranks alcohol third among preventable risk factors for premature death in developed nations. The extent of the alcohol use disorders problem in the U.S. and worldwide is summarized in Table I-5.

Table I-5. Extent of the Alcohol Use Disorder Problem

Globally:

* In 2003, the prevalence of alcohol use disorders was estimated at 1.7%, accounting for 1.4% of the total world disease burden in developed countries

United States:

* 18 million Americans (8.5% of the population age 18 and older) suffer from alcohol abuse or dependence. Only 7.1% of these individuals received any treatment for their alcohol problems in the past year.
* Alcohol problems cost U.S. society an estimated $185 billion annually
* Alcohol was the third leading cause of death in the US in 2003 (an estimated 85,000 deaths)

Source: World Health Organization, 2003

Alcohol also contributes significantly to mortality from a wide-range of acute and chronic injuries and diseases (see Table I-6). In the U.S. in 2001, 75,766 deaths were attributable to alcohol, 40,933 deaths were attributable to acute conditions primarily unintentional injuries such as motor vehicle injuries, and fall injuries, and intentional injuries such as homicide and suicide, and 34,883 deaths were attributable to chronic conditions especially alcoholic liver disease and liver cirrhosis. Because alcohol attributable deaths resulting from acute conditions occur earlier in the life span than chronic alcohol attributable deaths, they account for nearly twice as many years of productive life lost (e.g., 1,491,317) compared with chronic alcohol attributable deaths (e.g., 788,005).

Injuries are the leading cause of death in the U.S. from ages 1-44, and alcohol is the leading contributor to those injury deaths. It should be noted that many people who

die from alcohol attributable injury deaths are persons other than the drinker. For example, 40% of people who die in crashes involving drinking drivers are persons other than the drinking driver e.g. passengers in the same vehicle, passengers in vehicles struck by the drinking driver, bicyclists and pedestrians. Further, many homicide victims are fatally injured by persons who had been drinking. This underscores the need to identify, through rigorous research programs, policies that protect individuals from their own excessive drinking, as well as from the potential harms excessive drinking may cause society.

Table I-6. Number of deaths and years of potential life lost (YPLLs) attributable to the harmful effects of excessive alcohol use for selected conditions, by cause and sex – United States, 2001

	Deaths			YPLLs		
Cause	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
Chronic conditions						
Acute pancreatitis	370	364	734	7,138	6,054	13,192
Acute cardiomyopathy	443	56	499	10,195	1,552	11,747
Alcohol-induced chronic Pancreatitis	224	71	295	6,209	2,135	8,344
Alcoholic liver disease	8,927	3,274	12,201	221,369	94,952	316,321
Chronic pancreatitis	126	106	232	2,606	1,952	4,560
Esophageal cancer	394	53	447	6,213	788	7,000
Liver cancer	518	172	690	8,640	2,633	11,273
Liver cirrhosis, unspecified	3,917	2,802	6,719	80,616	54,528	135,144
Oropharyngeal cancer	303	57	360	5,280	889	6,169
Total	24,448	10,285	**34,883**	549,396	239,619	**788,005**
Acute conditions						
Alcohol poisoning	253	78	331	8,798	2,952	11,750
Homicide	5,963	1,692	7,655	262,379	71,543	333,922
Motor vehicle	10,674	3,000	13,674	442,943	136,558	579,501
Suicide	5,617	1,352	6,969	186,568	49,297	235,865
Falls	2,500	2,206	4,766	41,627	24, 288	65, 914
Total Acute Conditions	30,309	10,534	**40,933**	1,131,028	350,289	**1,491,397**
Total	54,947	20,918	**75,766**	1,679,414	599,908	**2,279,322**

Source: Adapted from the table in Alcohol-Attributable Deaths and Years of Potential Life Lost --- United States, 2001 MMWR September 24, 2004, 53;866-870.

Co-Morbid Conditions

In addition to the many adverse health effects that result directly from alcohol misuse, co-morbid conditions often present further complications for individuals with alcohol abuse problems. Alcohol abuse and dependence commonly occur in individuals who suffer from mood, anxiety, and personality disorders as well as the effects of other drugs of abuse, (see Table I-7). For example, an estimated 90% of cocaine addicts have alcohol problems. It also has been estimated that as many as 60% of patients presenting at community mental health centers have co-morbid alcohol and other drug

abuse disorders. Patients suffering from both disorders often have poorer treatment outcomes and are more likely to drop out of treatment. Unfortunately, effective pharmacological and behavioral treatments have yet to be established for the various conditions of co-morbid AUD and other drug abuse disorders.

The high co-morbidity between alcohol and tobacco dependence poses special problems. Fifty to ninety percent of alcoholics smoke, a rate that is three times higher than among the population as a whole. Alcoholics smoke heavily, are more addicted to nicotine and are less successful at quitting smoking, which puts them at a greatly increased risk for the synergistic effects of alcohol and nicotine on the development of certain cancers and cardiovascular diseases.

Table I-7. Odds of Current (past 12-month) DSM-IV Alcohol Dependence Co-Occurring with Selected Psychiatric Conditions

Disorder	Odds
Anxiety Disorders	2.6 x
Mood Disorders (especially Major Depression)	4.1 x
Personality Disorders	4.0 x
Antisocial Personality Disorder	7.1 x
Drug Dependence	36.9 x
Nicotine Dependence	6.4 x

Source: NIAAA 2001-2002 NESARC data

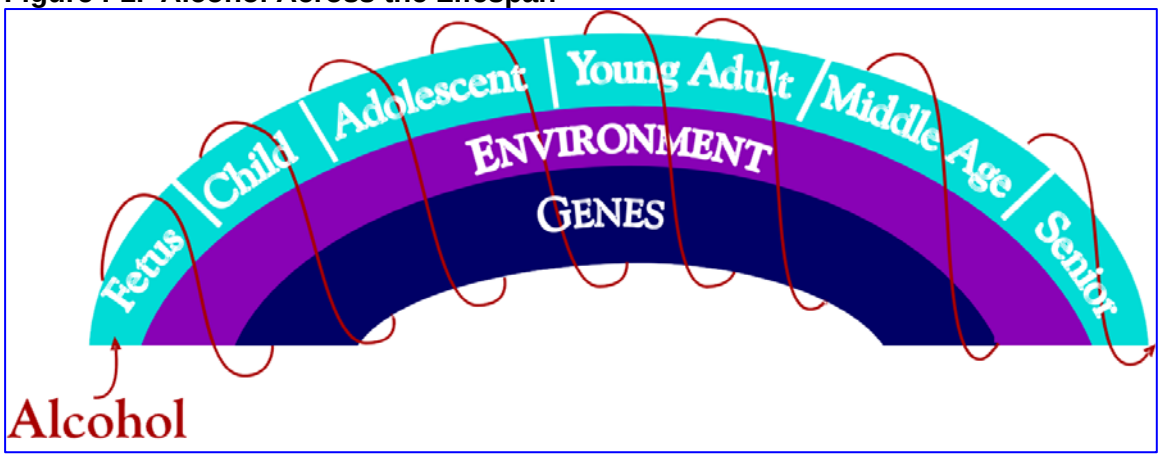
Contributions to Alcohol Use and Alcohol Problems Across the Lifespan

The initiation and continuation of alcohol use by an individual is influenced by numerous factors, chiefly the individual's genetic makeup, the environments to which he or she is exposed, and complex mechanisms through which genes interact with one another and with the environment. These same factors determine an individual's pattern of alcohol consumption and the risks for developing alcohol dependence (alcoholism) or other alcohol use disorders.

More than three decades of research has firmly established that genes account for more than half of the risk for alcoholism and environmental factors account for the remainder. This statement, however, belies the true complexity of the mechanisms underlying the risk for, and protection against, alcohol abuse and alcohol dependence. As with many other complex diseases, there is no single genetic or environmental factor that can fully account for the risk of alcoholism. The development of such complex behavioral and other medical disorders likely depends upon the specific genetic factors interacting with one another, the interaction of multiple environmental risk factors, and the interaction of genetic and environmental factors.

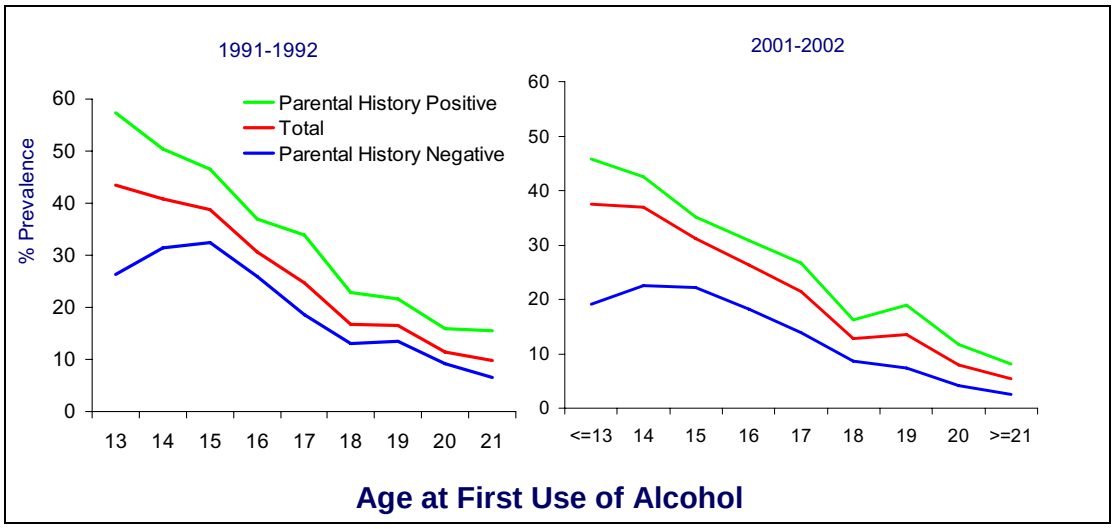
Research has also revealed that neither genetic nor environmental factors are static. That is, the emergence and progression of drinking behavior and of drinking consequences is influenced by multiple ongoing changes in biology, physiological and psychological development, and environment that occur over the course of a person's life. These observations are in accord with a broader recognition that human development continues throughout life, rather than stopping after adulthood is reached. A full understanding of the development of drinking behaviors and disorders, therefore, requires a lifespan context, in which the central concept is that the influence of alcohol on biology and behavior is dynamic and changes as an individual moves from childhood into adolescence and through the various stages of adulthood. This conceptual framework is depicted schematically in Figure I-1.

Figure I-1. Alcohol Across the Lifespan



Some of the first evidence of the importance of the lifespan perspective for understanding alcohol use disorders emerged less than ten years ago in an analysis of data derived from NIAAA's National Longitudinal Alcohol Epidemiologic Study (NLAES). This analysis indicated that persons who begin drinking at younger ages have a significantly increased risk for the development of alcoholism. This finding was replicated in the recent NESARC study, as shown in Figure I-2. These data show that young people who begin drinking before age 15 were four times more likely to develop alcohol dependence during their lifetime than those who begin drinking at age 21. This is true for individuals from families where a parent had a history of alcoholism (Parental History Positive) and for individuals with no parental history of alcoholism (Parental History Negative). Therefore, while parental history clearly contributes to the risk for developing alcoholism, likely a reflection of genetic risk factors, early initiation of drinking is also an important predictor of risk for the eventual development of alcoholism.

Figure I-2. Prevalence of Lifetime Alcohol Dependence by Age of First Alcohol Use and Parental History of Alcoholism



Source: NIAAA 1991-1992 NLAES data (left panel) and NIAAA 2001-2002 NESARC data (right panel)

What is the mechanism by which exposure to alcohol in youth or adolescence increases the risk for alcoholism? Early exposure to alcohol may alter neurodevelopment through one or more mechanisms to cause increased vulnerability to alcohol dependence. Alternatively, it is possible that some other biological factor, perhaps affecting personality, is responsible for both the early onset of drinking and the heightened risk for alcoholism. As research continues, new findings will help to establish how, and the extent to which each of these two potential mechanisms contribute to the development of alcohol problems. That knowledge will arise from research on brain development in general, as well as from research directed specifically to alcohol-related issues. For example, research on human brain development has revealed that the brain continues to develop through adolescence and into young adulthood. Research also has shown that adolescents in treatment for alcohol dependence have reductions in the size of a brain region known as the hippocampus. Taken together, these two findings provide support for the hypothesis that early alcohol exposure perturbs and thereby alters early brain development which contributes to later vulnerabilities for alcoholism and other disorders.

What is the prevalence of alcohol problems in other phases across the lifespan? As Table I-8 shows, the prevalence of alcohol abuse and alcohol dependence within the past year varies with age. The highest previous year prevalence of alcohol dependence is found among the young adult population (defined as 18-29 years of age), particularly between the ages of 18 through 24. As has been noted, problems with alcohol use disorders are also very significant in the adolescent population, aged 12-17 years (further discussed in Chapter III). From its peak in the young adult years, the prevalence of past year alcohol dependence declines with increasing age (adolescence, young adult, midlife defined as 30-59 years of age, and senior), falling below one percent among senior adults (defined as 60 years of age and older). According to these data, at any time point, the percentage of individuals who received treatment for their alcohol use disorder is quite small relative the numbers experiencing alcohol problems (also see Figure I-5).

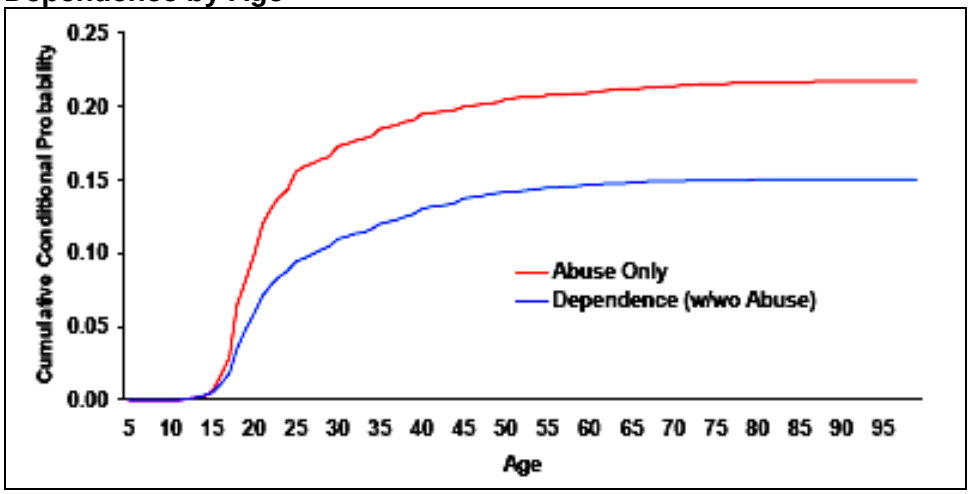
Table I-8. Percentage of U.S. Adults 18 and Over with Past-year Alcohol Abuse or Dependence and Percentage of Those with Past-year Abuse or Dependence Who Received Alcohol Treatment, by Type of Treatment

	Past-year disorder				Type of treatment							
Age group	Abuse		Dependence		Any treatment		12-Step only		Other only		12-Step and other	
All ages	4.7	(0.2)	3.8	(0.1)	7.1	(0.5)	1.1	(0.2)	2.7	(0.3)	3.4	(0.4)
Young Adult												
18-29	7.0	(0.4)	9.2	(0.4)	5.9	(0.7)	1.3	(0.4)	2.3	(0.4)	2.3	(0.5)
18-24	6.7	(0.5)	11.6	(0.6)	6.4	(0.9)	1.4	(0.5)	2.8	(0.6)	2.2	(0.6)
25-29	7.3	(0.6)	5.7	(0.4)	4.9	(1.2)	1.0	(0.5)	1.2	(0.5)	2.7	(0.9)
Midlife												
30-59	5.0	(0.2)	3.0	(0.2)	8.5	(0.7)	0.8	(0.2)	3.1	(0.5)	4.5	(0.6)
30-44	6.0	(0.3)	3.8	(0.2)	8.9	(1.0)	0.7	(0.2)	3.2	(0.7)	5.0	(0.8)
45-59	3.9	(0.3)	2.0	(0.2)	7.5	(1.2)	1.0	(0.4)	3.0	(0.8)	3.5	(0.8)
Senior												
60+	1.4	(0.1)	0.5	(0.1)	3.4	(1.3)	1.9	(1.1)	0.8	(0.6)	0.6	(0.4)

Source: NIAAA 2001-2002 NESARC data

Figure I-3 looks at the history of alcohol abuse and alcohol dependence from a cumulative life-time perspective. The figure shows the cumulative conditional probability that an individual at a given age would have at some point in their life met the diagnostic criteria for DSM-IV alcohol abuse or dependence. As seen from the figure, by age 30 these probabilities were 10% and 17% respectively for dependence and abuse. By age 60 they are 14% and 20% respectively.

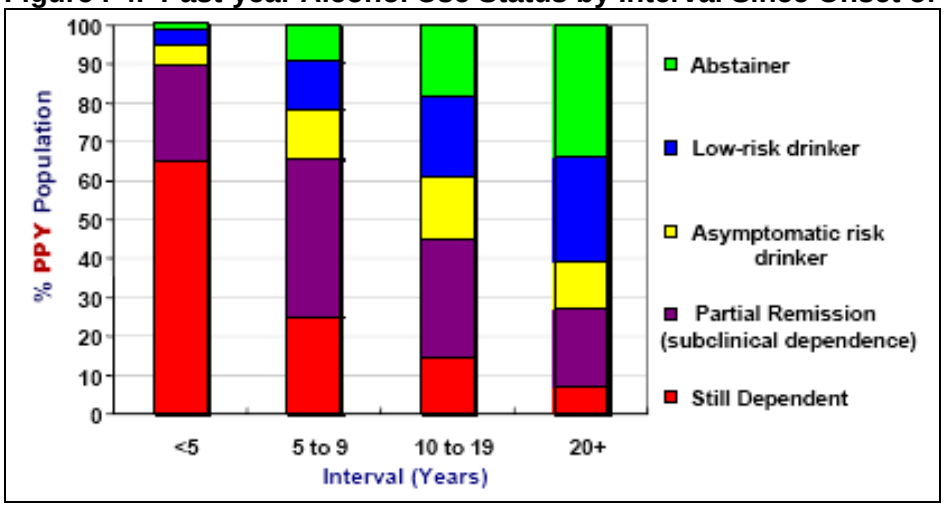
Figure I-3. Cumulative Probability of Onset of DSM-IV Alcohol Abuse or Alcohol Dependence by Age



Source: Substance Abuse and Mental Health Services Administration (SAMHSA) 2002 National Survey on Drug Use and Health (NSDUH) data (ages 12-17) and NIAAA 2001-2002 NESARC data (ages 18-60+)

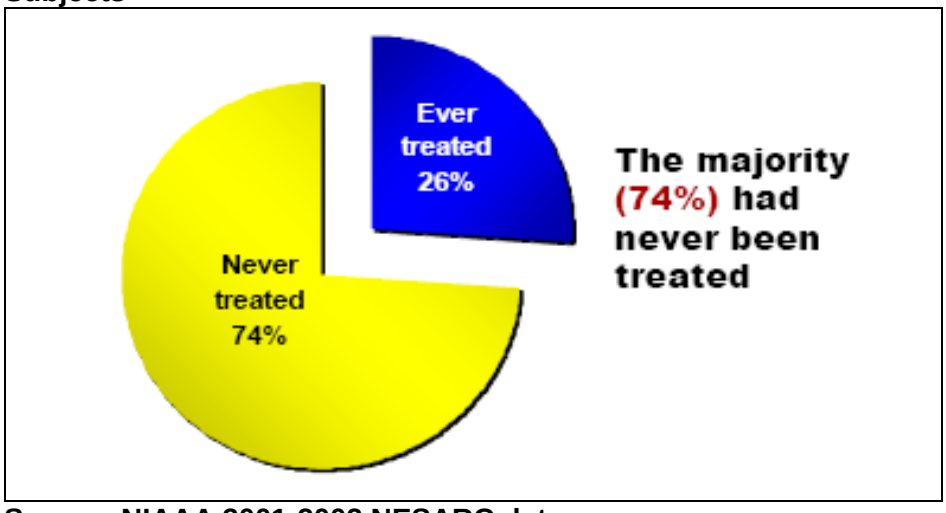
Figure I-4 examines this same data from NESARC, looking at the past-year status of drinking by the interval since the individual first met the diagnostic criteria for alcohol dependence. Less than 10% of the individuals interviewed met the criteria for past-year alcohol dependence 20 years or more after initially meeting dependence criteria. Of those individuals who initially met diagnostic dependence criteria less than 5 years previously, 65% still met the criteria for dependence. As the figure shows, over 30% of individuals who initially met dependence criteria 20 or more years previously were abstinent in the past year, but in this time-frame category, as well as the other time frames since dependence onset, some individuals in the past year were in partial remission (some but not all dependence or abuse symptoms), asymptomatic risk drinkers, or low risk drinkers (less than 5 drinks on any occasion or 14 drinks per week).

Figure I-4. Past-year Alcohol Use Status by Interval Since Onset of Dependence



Source: NIAAA 2001-2002 NESARC data

Figure I-5. History of Prior Interventions in Prior to Past Year Alcohol Dependence Subjects



Source: NIAAA 2001-2002 NESARC data

The changes in drinking status over time shown in Figure 1-4, coupled with the finding that 24.4% of individuals who had prior to the past year (PPY) alcohol dependence recovered without the benefit of alcohol dependence treatment provides evidence that some individuals may "age-out" or experience natural recovery from the disorder.

Alcohol-Related Policy and Public Health Outcome

A wide range of public policies may affect alcohol consumption and other behaviors relating to alcohol, and therefore can have important influences on public health outcomes. In the United States, laws, regulations, and jurisprudence address (1) alcoholic beverage production, packaging, transportation, marketing, taxation, sales, and consumption, (2) financing and delivery of alcohol-related treatment and preventive services, and (3) behaviors that may be affected by alcohol, such as driving and boating. In many of these topic areas, policies are established by governments at all levels (Federal, State, county, and municipal).

Scientific research has identified a number of alcohol-related policies that have significant effects on public health outcomes. Among the policies with the best evidence of effectiveness is the minimum legal drinking age of 21, which has been shown to reduce consumption and traffic crash deaths among youth 16-21. This policy may also have other benefits, as studies have shown that deferring the initiation of drinking reduces both the risk and severity of subsequent alcohol use disorders. Although every state now sets the minimum age for possession and purchase of alcoholic beverages at 21, there is still substantial variation in states' policies toward underage drinking. Many states afford significant exceptions to the laws against possession and consumption (e.g., except for in a private residence, or only in a public place).

Policies addressing drinking and driving have been shown to reduce traffic fatalities. Every State has now established a law against driving with a blood alcohol concentration (BAC) of .08 or above. All States have also adopted so-called "zero tolerance" laws that set BAC limits for drivers under the age of 21 at no more than .02 percent. These laws, combined with a variety of other policies designed to deter driving after drinking, have helped reduce rates of alcohol-related traffic fatalities in the United States by 50% since 1982.

Alcoholic beverage taxes are another policy for which there is strong evidence of effectiveness. Although tax rates are most often established for fiscal rather than public health purposes, a number of studies have found significant relationships between higher taxes on alcoholic beverages and lower rates of traffic crash fatalities or drunk driving, particularly among younger drivers or during nighttime hours. Other research has found associations between higher alcoholic beverage taxes and lower rates of some types of violent crime, reduced incidence of physical child abuse committed by women, and lower rates of sexually transmitted diseases and liver cirrhosis mortality, as well as with increases in college graduation rates.

Public policies affecting the delivery and financing of alcohol-related treatment and preventive services may have important effects on access to treatment services.

Most states now require health insurers to cover treatment for alcoholism, and a number of other states require such coverage to be offered but not necessarily included in every insurance contract. However, no Federal laws require coverage for alcoholism treatment, and Federal law exempts many large employers from state laws with such requirements. As a result, many insurance policies may not include coverage for alcoholism treatment.

Many states have laws, known as "Uniform Accident and Sickness Policy Provision Laws," or UPPL, that permit health insurers to deny payment for losses that are the result of the insured person being intoxicated. Researchers have suggested that these policies create a disincentive for health care providers in emergency and primary care settings to screen for alcohol problems, with the result that fewer individuals in need of treatment for alcohol problems are referred to treatment just when such referrals might be most effective. While studies have not yet established the true effects of UPPL provisions on treatment referrals, a few states have recently enacted laws that prohibit exclusion of insurance benefits on the basis of intoxication.

Because of the complexity of alcohol-related public policies, researchers face a challenge in identifying how specific policy measures may affect health outcomes. The Alcohol Policy Information System (APIS), developed by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), provides reliable, detailed, and comparable information on alcohol-related public policies in the United States at both the state and Federal levels. The APIS Web site (http://alcoholpolicy.niaaa.nih.gov) provides public access to detailed information on a wide variety of alcohol-related public policies. Intended primarily as a tool for researchers, APIS features compilations and analyses of alcohol-related statutes and regulations designed to simplify the process of ascertaining the state of the law for studies on the effects and effectiveness of alcohol-related policies

D. Issues that Transcend the Lifespan Perspective

There are four issues that provide significant background perspectives necessary for the accurate interpretation of previous results and the formulation of research hypotheses with respect to alcohol use across the lifespan. These issues are alcohol metabolism, alcohol and gene/environment interactions, the neurobiology of alcohol, and the diagnostic criteria for alcohol abuse and dependence. They are presented in this overview as they transcend the full lifespan.

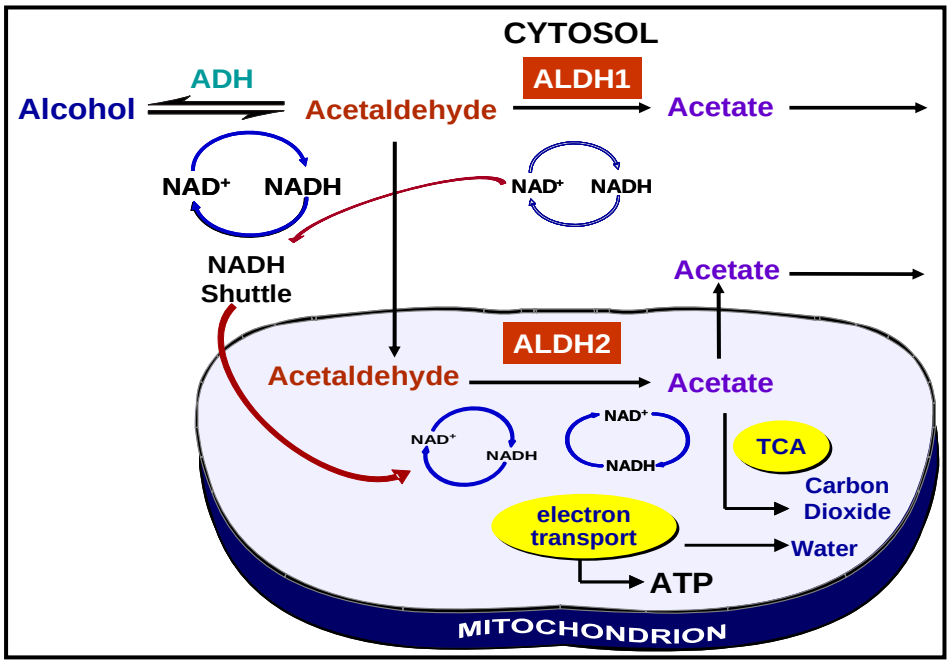
D.1. Alcohol Metabolism

Individuals differ in how fast they metabolize alcohol (pharmacokinetics) and in the extent to which they are affected by a given dose of alcohol (pharmacodynamics). These individual differences affect drinking behavior, the potential for the development of alcohol dependence, and the risk for developing alcohol-induced organ damage. Therefore, understanding these differences will provide important information about alcohol's health effects throughout the lifespan.

The major pathway for the metabolism of alcohol is found in the liver and involves the enzyme alcohol dehydrogenase (ADH) (see Figure I-6). Alcohol is metabolized to acetaldehyde, a highly reactive and potentially toxic molecule. In most circumstances, acetaldehyde is rapidly metabolized by another enzyme, aldehyde dehydrogenase (ALDH) to acetate. Because of the rapid enzymatic conversion of

acetaldehyde to acetate, the concentration of acetaldehyde in the cell is typically a thousand-fold lower than that of alcohol, and the eventual product of this pathway, acetate. Both alcohol and acetate are found at millimolar levels following drinking, while acetaldehyde is found at micromolar concentrations. [The legal intoxicating blood alcohol level in all states in the U.S. is 80 mg%, which is 17.4 mM. The normal baseline level for acetaldehyde in humans is 9 µM, or 40 µgram%. After alcohol ingestion, the acetaldehyde level in most individuals will increase to 20-30 µM, or 90 – 130 µgram%. Metabolism of a dose of alcohol achieving a blood alcohol concentration of 80 mg% may result in elevation of tissue acetate levels by 100 mg%.] When the level of acetaldehyde increases, an individual may experience very dysphoric feelings and the potential for toxic reactions with various cellular components increases.

Figure I-6. Alcohol Metabolism in the Liver



Source: Figure created by Brenda Hewitt

There are a number of variants of the ADH and ALDH enzymes, and the differences in the profile of the variants present can influence an individual's drinking behavior. The various functional variants of ADH and ALDH are shown in Table I-9.

Table I-9. Human ADH and ALDH Isozymes

	Class	Nomenclature	Km (mM)	$V_{max}(min^{-1})$
Alcohol Dehydrogenase (ADH)	I	ADH1A	4.0	30
		ADH1B*1	0.05	4
		ADH1B*2	0.9	350

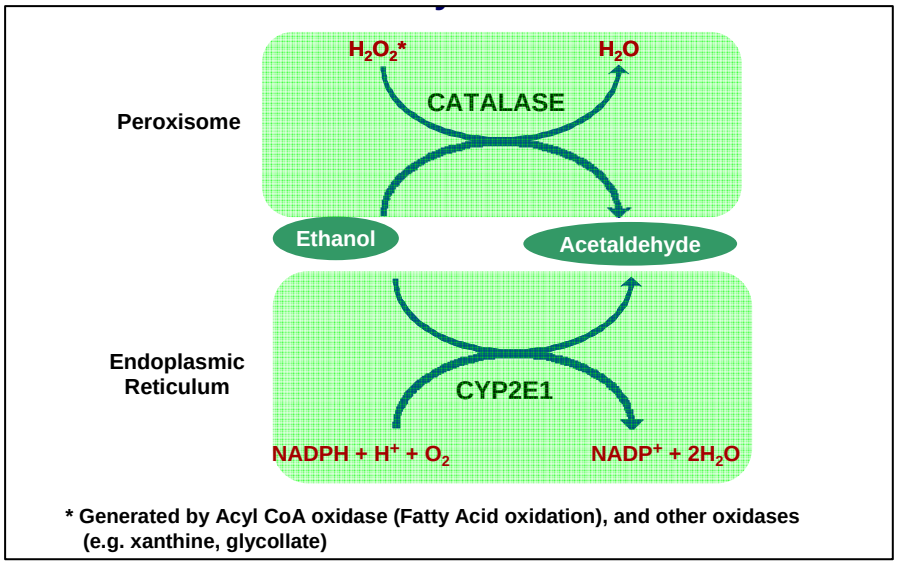
		ADH1B*3	40.0	300
		ADH1C*1	1.0	90
		ADH1C*2	0.6	40
	II	ADH4	30.0	20
	III	ADH5	>1000	10
	IV	ADH7	30.0	1800
	V	ADH6	?	?
Aldehyde Dehydrogenase (ALDH)		ALDH2*1	3	0.4
		ALDH2*2	~300	--

Source: ADH: Km and V_{max} values from Hurley et al., 2002; ALDH V_{max}: Yin & Li (pp. 227-247), In Sun et al., Molecular Mechanisms of Alcohol: Neurobiology and Metabolism, Humana Press, 1989; ALDH Km: Mizoi et al., 1994.

Most of the alcohol consumed by humans is metabolized by the Class I and Class II ADH enzymes (Table I-9). While only one functional form of the Class II ADH is known, the Class I ADHs exist in a number of polymorphic forms, and differences in individual Class I ADHs contribute to variation in the alcohol metabolic rate (Table I-9). Of particular importance are the three known functional variants of *ADH1B.* The *ADH1B*2*, found in the majority of Asians and 25 percent of people of Jewish ancestry, and the *ADH1B*3*, found in some African Americans, oxidize alcohol at a faster rate than the *ADH1B*1* variant which predominates in most European Americans. Two functional forms of the *ADH1C* gene also exist (*ADH1C*1* and *ADH1C*2*). The Class I ADH enzymes are found primarily in the liver in the cytosol compartment of the cell.

There are other enzyme pathways that can metabolize alcohol to acetaldehyde, including cytochrome P450 and catalase (Figure I-7). The cytochrome P450 isozyme CYP2E1 is the form which is predominantly involved in alcohol oxidation. It is present in an internal cellular structure known as the endoplasmic reticulum and particularly comes into play after chronic, heavy, alcohol exposure. Alcohol metabolism by CYP2E1 also produces highly reactive oxygen species (ROS) with the potential to cause tissue damage. Unlike most Class I ADH enzymes that are primarily found in the liver, CYP2E1 is found in a number of tissues and organs including liver, brain, heart, lung, and the neutrophils and macrophages of the immune system. Therefore, the generation of acetaldehyde and ROS within these tissues poses risks for injury to these systems. The enzyme catalase (Figure I-7), located in the intracellular structure known as the peroxisome, is also capable of oxidizing alcohol in the presence of a hydrogen peroxide (H_2O_2)-generating system. However, catalase appears to be a minor pathway for alcohol metabolism.

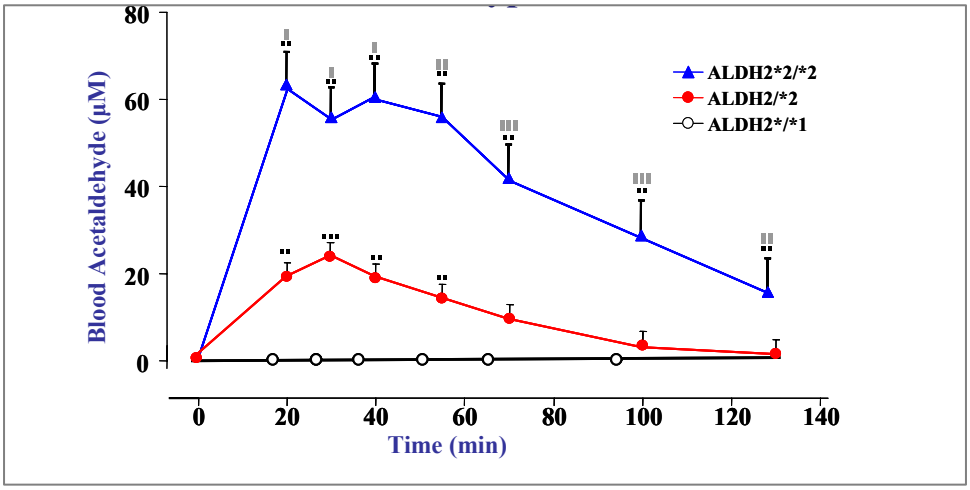
Figure I-7. Minor Oxidative Pathways of Alcohol Metabolism



Source: Figure created by Dr. Ting-Kai Li and Dr. Samir Zakhari.

The acetaldehyde that is produced from alcohol oxidation through any of these enzyme systems is typically metabolized rapidly to acetate. ALDH catalyzes the oxidation of many aldehydes, and under conditions of ethanol exposure, ALDH enzymes specifically convert acetaldehyde to acetate. Genetic polymorphisms in the ALDH genes have been linked to decreased risk of alcoholism and increased risk of alcohol-induced cancers. A variant of the mitochondrial aldehyde dehydrogenase enzyme *(ALDH2*2)* is found in about 50 percent of Taiwanese, Han Chinese, and Japanese populations. The enzyme expressed by *ALDH2*2* is virtually inactive. Consequently, individuals with one, and particularly two copies of this allele show elevations in acetaldehyde after consuming alcohol (see Figure I-8). Individuals with both *ADH1B*2* and *ALDH2*2* genes have been shown to have virtually complete protection against developing alcoholism, presumably due to the adverse effects of elevated acetaldehyde. This allelic combination is curiously absent in Native American Indian populations, who have a high prevalence of alcoholism, suggesting that other combinations of ADH and ALDH genes may confer various forms of protection or susceptibility to alcohol use disorders.

Figure I-8. Blood Acetaldehyde Concentrations of Han Chinese Men with Different ALDH2 Allelotypes (0.2 g/kg ethanol)



Source: Chen et al. Interaction between the functional polymorphisms of the alcohol-metabolism genes in protection against alcoholism. Am J Hum Genet 65:795-807, 1999

Most of the acetate arising from ethanol metabolism departs the liver via the circulatory system and is eventually metabolized to carbon dioxide (CO_2) and water by way of the tricarboxylic acid cycle (TCA) in heart, skeletal muscle, brain, and liver. Further, acetate itself is not an inert product; in addition to being a metabolic source of energy, it can increase portal blood flow in the liver, and potentially in other organs, and contributes to the biosynthesis of adenosine which has its own effects on cortical and coronary blood flow in response to need.

The oxidation of alcohol through ADH, and acetaldehyde through ALDH, is accompanied by the conversion of the co-enzyme nicotinamide-adenine dinucleotide (NAD^+) to its reduced form NADH (Figure I-7). When sufficiently large amounts of alcohol are consumed, alcohol metabolism can change the reductive-oxidative state of the cell (redox state), expressed as the ratio of NAD^+/NADH. The change in the NAD^+/NADH ratio, in turn, can affect a number of metabolic pathways within the cell. Further, the NADH generated through alcohol and acetaldehyde oxidation is subsequently re-oxidized to NAD^+ through the mitochondrial electron transport chain, a process that involves the generation of the energy intermediate ATP. Enzymes within the electron transport chain also have the potential to generate ROS. In a cellular environment low on antioxidant defense mechanisms (e.g., glutathione), such as occurs after heavy alcohol exposure, these ROS have the potential to disrupt developmental processes and to cause tissue damage.

In addition to the oxidative pathways of alcohol presented above, alcohol can also be non-oxidatively metabolized by at least two pathways. One leads to the formation of fatty acid ethyl esters (FAEE) and the other to phosphatidyl-ethanol. Both oxidative and non-oxidative pathways of alcohol metabolism are inter-related, and may result in tissue injury throughout the lifespan.

Opportunities for Research in Alcohol Metabolism Across the Lifespan

- The field of metabolomics has increased in depth and breadth during the last five-year period, and there is an emerging opportunity to explore how

changes in metabolism affect brain, other organs, and functional outcomes of alcohol use on all ages of individuals. The products of this research may further uncover the mechanisms by which alcohol is involved in the development of pathologies at all stages of the lifespan, from the fetus to the elderly, and may lead to the identification of biomarkers for early pathology recognition thus facilitating more effective intervention and treatment implementation.

- Enhance understanding of the differences in alcohol *pharmacokinetic*s (the rate by which an individual metabolizes alcohol) and *pharmacodynamics* (the extent to which an individual is affected by a given dose of alcohol) in their respective contributions to alcohol dependence and organ pathologies arising from alcohol use.

- Identify metabolic profiles that provide an early indication of alcohol use disorders and alcohol-derived pathologic diseases.

- Continue to investigate how alcohol alters the oxidative state of the cell, the pathologic consequences of the changes in oxidative state, and mechanisms by which alcohol alters the cellular defenses against oxidative damage.

D.2. Alcohol and Gene/Environment Interaction, and Epigenetics

Neither genes nor environment alone can explain why any particular individual develops alcohol dependence. Rather, as a complex disorder, risk for the development of alcohol dependence will be a consequence of the interplay of multiple genes, potentially multiple environmental factors, and the interaction of these genes and the environmental factors. Similarly, it is not likely that any single mechanism of gene-environmental interaction will explain all vulnerability to alcohol dependence. While in the past decade investigators have sought to define both genes and environmental factors underlying risk, this effort had been limited due to a lack of powerful technologies and methodologies that could be applied to the genetic study of complex disorders such as alcoholism. In recent years, advanced technologies such as single nucleotide polymorphisms (SNPs) and haplotype maps have enabled scientists to identify genes associated with these disorders. Although a few genes, such as GABRA2, ADH, ALDH, CHRM2, OPRM1 and NPY, have been linked to alcohol dependence and its related disorders, it is apparent that more genes will be rapidly identified. A number of candidate genes in animals and humans are presented in Table I-10.

Table I-10. Genes Contributing to Alcohol-Related Behaviors in both Rodents and Humans

Gene	Rodent	Human
a-synuclein	QTG for alcohol preference (Liang et al., PNAS 2003)	associated with alcohol dependence (Bonsch et al., Hum Mol Genet. 2005)
BDNF	BDNF levels in the NAc are lower in P rats than NP rats (Yan et al., Brain Res. 2005)	association of val66met polymorphism with alcohol dependence & violence in males (Tsai et al., Neurosci Lett. 2005)
NMDA NR1	Mutant mice show attenuated alcohol effects on behavior (Kiefer et al., Biol Psychiatry 2003)	the A allele is associated with type I alcohol dependence (Wernicke et al., Biol Psychiatry. 2003)
CB1	KO showed ↓ alcohol consumption (Hungund et al., J Neurochem 2003)	1359G/A polymorphism confers vulnerability to alcohol withdrawal (Schmidt et al., Drug Alc Dep. 2002)
CCK-AR	KO showed ↑ alcohol consumption (Miyasaka et al., Alcohol & Alcohol 2005)	-81A/G polymorphism is Associated with alcohol dependence in a Japanese population (Miyasaka et al., Alcohol & Alcohol 2004)
5-HTT	Alcohol intake ↓ in KO mice (Kelai et al., Alcohol Alcohol 2003)	Associated with lower risk of binge drinking (Olsson et al., Mol Psychiatry 2005)

The search for both genetic and environmental risk factors includes both human population genetics investigation, as well as studies involving animal models. Specifically, selected animal strains are used to model the endo- and intermediate phenotypes (see Table I-11) involved in the development of human alcohol dependence. While animal models of alcohol tolerance and alcohol preference have been developed in the past, refinement of current models is still required in order for them to more closely parallel those features of the clinical syndrome phenotype, including modeling such contributing traits as anxiety, propensity for relapse, and obsessive-compulsive behaviors such as craving.

Table I-11. Definition of Endophenotype, Intermediate Phenotype, and Clinical Syndrome Phenotype

Endophenotype: innate or biological host factors that may predispose an organism to alcohol dependence (e.g., temperament, gene expression, electrophysiology, developmental biology)

Intermediate phenotype: host factors interact with environmental factors to facilitate the development of alcohol dependence (e.g., sensitivity, tolerance, reward)

Clinical Syndrome Phenotype: the transition from voluntary to nonvoluntary, obsession with and compulsion to use alcohol

Epigenetics

One additional route by which alcohol may affect the development of alcohol disorders, from alcohol dependence to organ disease is through epigenetics, which refers to stable alterations in the genome, sometimes heritable through cell division, that do not involve permanent changes to the DNA sequence itself. Epigenetic processes

act as an additional source of biologic variation beyond that attributable to the genetic code. These processes involve the chemical modification of the constituents of the chromosome, the DNA molecules and the gene-regulating proteins known as histones, and may occur as a consequence of exposures to specific environmental substances and stimuli. Alcohol and its metabolites could be important environmental factors contributing to epigenetic processes. For example, alcohol has been shown to cause acetylation at specific histone sites in the rat chromosome, resulting in increased expression of the ADH gene. Further, alcohol has the ability to alter the normal biochemical pathways by which DNA and histones might be modified in response to other events occurring in the environment. For example, alcohol can interfere in the metabolic pathways leading to the biosynthesis of the intermediates required to modify DNA, by altering biosynthetic pathways involving folate, and inhibiting the synthesis of a "methyl donor" known as S-adenosyl methionine (see Figure V-1 in Chapter V).

Related to such metabolic alterations, alcohol may influence epigenetic processes in ways opposite to that necessary for normal functioning, and in the case of the fetus, to that required for normal development. Epigenetic events also may contribute to the development of alcohol tolerance and sensitization, obsessive-compulsive drinking, craving, cognitive effects of chronic drinking and organ damage associated with heavy drinking.

Opportunities for Exploring Alcohol and Gene/Environment Interaction, and Epigenetics Across the Lifespan

There are many opportunities to explore the effects of alcohol exposure on the interaction of genes and environment across the lifespan, even though the effects of heavy alcohol consumption may differ significantly given the age of exposure, and with respect to alcohol's direct or indirect effects.

- The contribution of animal models to genetics research is limited by the relevance of current animal models to the actual phenotype of human alcohol dependence. The technologies exist to develop new animal strains that model both the endophenotypes (e.g., electrophysiological trait risk factors) and intermediate phenotypes (e.g., cue response to alcohol) associated with alcohol exposure. New animal models may also be developed through resources emerging from the NIH Roadmap and the Neuroscience Blueprint including animal knock-out lines, knock-in lines, and transgenic animals, where specific pathways involved in the CNS actions of alcohol are altered. These lines can be subjected to genetic analysis for uncovering key pathways involved in the development of alcohol dependence.

- Work to incorporate alcohol-related measures, including alcohol use disorders, family history of alcoholism, and detailed measures of alcohol consumption, into the National Health and Nutrition Examination Survey (NHANES) so future efforts can be undertaken to study the effects of interactions between alcohol-related measures and environmental factors such as diet, physical activity, smoking, and exposure to toxins, on risk factors for chronic disease.

- As new and more powerful approaches to genetic analysis emerge from the Human Genome Program and the NIH Roadmap, these technologies, including whole genome SNP and haplotype scans, new methods for quantitative trait gene identification, may be applied in both human population

genetics research and on animal model studies in the identification of genes contributing to the risk for alcohol disorders.

- Exploit the use of twin registries (e.g., identical twins discordant for disease) and existing cohorts of twins (e.g., Australia's cohort) to identify relative weight of gene/environment influence in developing alcohol dependence or alcohol abuse

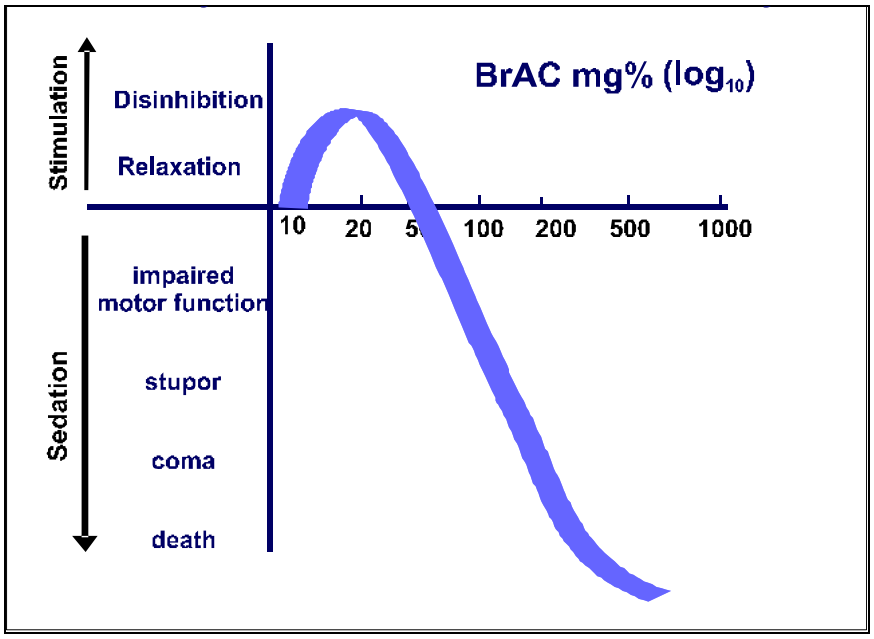
- The effect of alcohol on epigenetic processes typically involves undesirable changes in gene expression that have the potential to alter anatomy, function, and risk of disease at any age. For example, there may be direct effects of alcohol on fetal development, resulting in the characteristic FAS facial features, or the effect of alcohol on maternal gene expression at or near conception which may alter embryo survival or result in severe birth defects to the fetus. In alcohol consuming youth, the effects of alcohol may be to alter the expression of specific genes controlling the growth and maturation of organs (including brain). Adults may also experience the direct effects of alcohol through epigenetic mechanisms with consequent organ and tissue damage. The study of epigenetic mechanisms on phenomena across the lifespan can provide valuable insights into the mechanisms by which alcohol contributes to both the development of alcohol dependence and of other alcohol-related pathologies.

D.3. Neurobiology of Alcohol

Since the brain is a significant target for alcohol-induced toxic effects, and the brain undergoes development and maturation continuously from conception to birth and into adulthood, the effects of alcohol on neurobiology and neural processes in general are observed throughout life. Therefore, at any point in the lifespan, alcohol consumption may affect the normal physiology of the CNS, which makes the topic of alcohol's detrimental effects on the brains of any age of importance for comprehensive examination.

Alcohol has complex pharmacodynamic effects on the body, primarily through its interactions with the brain within the central nervous system (CNS). Alcohol's pharmacologic effects typically begin with mild stimulation, followed by CNS depression as shown in Figure I-9. Disinhibition and anxiolysis may also be experienced in the early phase following alcohol ingestion. As is noted in Figure I-9, as breath alcohol concentration (BrAC) increases, the likelihood and severity of functional impairments increases, ranging from impaired motor function to respiratory depression and death.

Figure I-9. Pharmacodynamics of Ethanol on the Central Nervous System



Among the physiological or behavioral consequences of chronic alcohol use, that is, *drinking too much, too fast and/or too often*, are the disorders of alcohol abuse, and alcohol dependence. However, there are other pathologic consequences to both the CNS and the peripheral nervous system (PNS) that can arise from drinking over long periods of time. These usually do not clinically manifest themselves until the midlife period. Alcohol neurotoxicity can result from heavy alcohol consumption beginning as early as adolescence, which may be critical to understanding why certain individuals drink excessively and what biological factors continue to prompt them to drink. Furthermore, alcohol neurotoxicity affects the fetus with long-term consequences. Therefore, a discussion of alcohol's effect on the brain involves all ages of individuals.

Alcohol's effect on the brain can have immediate, direct, and wide-ranging ramifications, from effects on normal physiology (patterns of sleep-wake, thermoregulation), to effects on basic motor functions (balance, gait, coordination), to effects on thoughts and emotions (cognition). Of particular interest are physical or chemical alterations in the brain that may cause changes in cognition leading to a variety of responses that manifest as, for example, the decision to start or stop drinking alcohol or the decision to seek help for an AUD. The adaptations that occur in the development of alcohol dependence occur within the CNS as well. Therefore, it is important to explore the effects of alcohol on the brain at many levels, from cellular and molecular biology to cognitive effects, using the range of techniques and methods of neuroscience. Some relevant research topics that may advance the knowledge about the effects of alcohol on brain include an examination of synaptic protein adaptation, the differential temporal vulnerability (differences across the lifespan) of various brain regions and neuronal cell types to long-term consequences of alcohol-induced toxicity, changes in frontal lobe function associated with alcohol-induced cognitive alterations, impairments of neuroimmune and neuroendocrine function that predispose individuals to organ damage, and neuronal plasticity. These areas can be approached from a variety of perspectives in both clinical (human) and experimental (animal models) settings using

imaging and functional imaging, electroencephalography, and cellular and molecular biology techniques.

Opportunities for Examination of the Neurobiology of Alcohol Across the Lifespan
The central nervous system is a major target for adaptive, as well as toxic effects of alcohol across the lifespan, e.g., alterations in developing neurons, changes in neurotransmitter systems that alter neuronal function. Therefore, there is a wealth of information to be gained from researching the basics of the neurobiology of alcohol across various ages of subjects and experimental systems.

- Alcohol can directly affect the brain among those who drink excessively in terms of physical anatomy, and this has the end consequence of changes in function. One technical method that is relatively new for investigators in this field is diffusion tensor imaging, a form of magnetic resonance imaging (dtMRI). This technique allows a visual tracking of changes in white matter tracts in the brains of humans at any age. For example, fetal exposure to alcohol can result in alterations to the corpus callosum (a large fiber bundle connecting the two halves of the brain), while changes in the chemical constituents of white matter from alcohol exposure may accelerate the progression of white matter-specific diseases. Furthermore, excessive alcohol consumption in youth and young adults could significantly affect the *maturation* of their white matter ultimately leading to changes in neural circuitry (communications) involved in decision-making abilities and other aspects of altered cognitive function.

- Alcohol also affects neurotransmitters, their receptors and transporters, which are involved in neural communication and in brain development (in fetus). Alcohol-induced depletions of specific neurotransmitters have been shown to affect the development of specific brain regions in experimental animal models, while changes in the levels of neurotransmitters affect global neuronal communication. In addition to alcohol dependence, these changes may contribute to the expression of disorders co-morbid with alcoholism such as depression and anxiety. Technologies have emerged for improved quantification of alcohol's effects on neurotransmitters, receptors and transporters at all ages, including senior adult.

- Define the full range of *pharmacodynamic* effects of alcohol on central nervous system function and the variability associated with unique genetic and gene-environment profiles.

D.4. Diagnostic Criteria for Alcohol Abuse and Dependence

Since the early 1900s, numerous definitions of AUDs have been proposed. Currently, in the United States, the clinical standard used for defining and diagnosing AUDs is the American Psychiatric Association's Diagnostic and Statistical Manual, Fourth Edition (DSM-IV).

Definitions of alcohol abuse (see Table I-1) and dependence (see Table I-2) appearing in the DSM-IV both describe maladaptive patterns of alcohol use leading to clinically significant impairment or distress.

DSM-IV alcohol abuse requires at least one of the following four symptoms to occur within a 12-month period:

- drinking resulting in failure of the affected individual to fulfill major role obligations,
- recurrent drinking in situations in which it is physically hazardous,
- recurrent alcohol-related legal problems, or
- continued drinking despite social or interpersonal problems.

DSM-IV alcohol dependence requires that at least three of the following seven criteria be met:

- tolerance,
- withdrawal or relief drinking,
- drinking in larger amounts or for longer periods than intended,
- persistent desire or unsuccessful attempts to cut down or stop drinking,
- much time spent in obtaining alcohol, drinking, or recovering from its effects,
- important social, occupational, or recreational activities given up in favor of drinking, or
- continued drinking despite knowledge of physical or psychological problems caused or exacerbated by drinking.

Several issues have been raised concerning the applicability of the DSM-IV diagnostic definitions. With regard to dependence, the categorical nature of the diagnosis has been criticized as failing to represent the degree of severity inherent in the phenomenon. Each diagnostic symptom criterion carries equal weight in the classification, when clearly some criteria subsume symptoms that are more severe or disabling than others. The DSM-IV dependence diagnosis has also been questioned due to the absence of alcohol consumption measures, especially those consumption measures that have been found to increase individuals' risks for a variety of physical and psychiatric disorders related to excessive drinking. To address these issues, research has begun to focus on developing quantitative representations of AUD diagnostic criteria using statistical methods that provide differential severity weighting for individual AUD symptoms and allow for the inclusion of alcohol consumption variables.

Many contemporary researchers have also questioned the arbitrary differentiation between the DSM-IV alcohol abuse and dependence categories. Determining whether abuse and dependence symptom criteria represent distinct dimensions, or are related to the same underlying dimension or construct, will be important in future nosologic work in this area.

Another important issue related to the current DSM-IV formulation of alcohol abuse and dependence concerns the relevance of some of the criterion items to certain subgroups of the population. For example, some researchers have questioned the applicability of DSM-IV symptom items to females, a result of the historical definitions of diagnostic criteria based on clinical samples that have been composed largely of middle-aged males. The need to determine if differential case identification for AUDs exists for males versus females will be paramount for future prevention and intervention efforts. Biases attributable to language, differences in response tendencies (e.g., trait desirability, social approval, or acquiescence), or cultural expectations and experiences can also lead to differential reliability and validity of the AUD diagnoses across race-ethnic subgroups of the U.S. population. Further, questions have been raised about the

applicability of specific diagnostic symptom items across the lifespan, particularly among youth, young adults, and the elderly. Whether some symptoms of AUDs may be more relevant to different stages of the life course is an important research question. Given the relationship between early-onset drinking and the increased risk of developing an AUD, identifying criterion symptom items specific to youth and young adults will be critical to prevention and intervention efforts. Similarly, identifying AUD symptoms of greatest relevance in the elderly can increase our ability to recognize serious alcohol problems among this important subgroup of the population, which is projected to increase dramatically over the next 10 years.

Opportunities Related to the Diagnostic Criteria for Alcohol Abuse and Dependence

- Develop continuous representations of AUDs, with particular emphasis on severity and the inclusion of additional diagnostic criteria related to alcohol consumption measures.

- Identify differential case ascertainment for AUDs with respect to age, sex, and race-ethnicity, and determine if differences exist in the expression of AUDs among these subgroups of the population.

- Develop biomarkers for chronic alcohol use employing such technologies as glycoproteomics and other metabolites such as fatty acid ethyl esters (lipidomics).

CHAPTER II. The Embryo and Fetus

A. Background

The earliest stages of life, in particular, embryonic and fetal development, are periods of great vulnerability to the adverse effects of alcohol. A known teratogen (an agent capable of causing physical birth defects), alcohol may also damage neurological and behavioral development even in the absence of obvious physical birth defects. Alcohol's teratogenic effects were recognized over three decades ago, and it is now the leading known environmental teratogen.

Ranging from mild to severe, alcohol-induced birth defects are known as *fetal alcohol spectrum disorders* (FASD). The severity of defects depends on the dose, pattern, and timing of *in utero* exposure to alcohol. Research in animal models has demonstrated that the potential for adverse effects increases with the maternal blood alcohol concentration (BAC). As such, the peak dose, as measured by BAC, is a more important determinant of harm than is the total dose consumed.

The most serious adverse consequence of prenatal alcohol exposure is *fetal alcohol syndrome* (FAS), a devastating developmental disorder characterized by craniofacial abnormalities, growth retardation, and nervous system impairments that may include mental retardation. Children and adults with FAS have irreversible neurobiological deficits that affect multiple systems, ranging from motor control to executive function. Consequently, many secondary disabilities may occur, such as learning disabilities, attention disorders, failure in school, poor social skills, delinquent or criminal behavior, psychiatric co-morbidities, and premature and/or promiscuous sexual activity. Prenatal alcohol exposure itself may be a risk factor for subsequent alcohol and other drug use disorders later in life. The disabilities of FAS are life-long and place heavy emotional and financial burdens on individuals, families, and society.

Another *fetal alcohol spectrum disorder* is *partial FAS*, which includes the facial and neurodevelopmental deficits of FAS but not the growth deficits. Other FASD outcomes include *alcohol-related birth defects* (ARBD), where physical attributes of FAS are seen in the absence of the full syndrome, and *alcohol-related neurodevelopmental disorder* (ARND) in which neurobehavioral deficits are consistent with FAS, but the facial or physical features of FAS are absent.

By virtue of the lifelong learning and neurobehavioral deficits that characterize FAS and other types of FASD, many consider the central nervous system to be most critically affected by prenatal alcohol exposure. Imaging and neurobehavioral research in individuals with FAS and FASD reveals that some brain regions appear to be most sensitive to prenatal alcohol while other areas apparently are spared adverse effects. Particularly vulnerable regions include the frontal cortex, hippocampus, corpus callosum, and components of the cerebellum, including the anterior vermis. Obviously, the extent of damage to any brain area may be related to the timing of alcohol exposure relative to the rapid development or neurogenesis of a particular brain region, and the stage of embryonic development.

Epidemiological studies have revealed other adverse outcomes of prenatal alcohol exposure, including an increase in the risk for spontaneous abortion, pre-term delivery, stillbirth, and sudden infant death syndrome (SIDS).

B. Epidemiology

Despite alcohol's potent teratogenicity, only a small proportion of women who drink heavily give birth to children with FAS. The prevalence of FASD and FAS are presented in Table II-1 for selected countries. In the U.S., the prevalence of FAS has been estimated at 0.5-2.0 cases per 1000 births, with FASD projected to occur at several times that prevalence (10 per 1000 births). In some parts of the world the rate of FAS is far greater than in the U.S. This is particularly true in countries where alcohol consumption during pregnancy is more common than in the U.S. For example, in parts of South Africa, where farm wages once were paid in part, with alcohol, a heavy drinking culture is quite prevalent among the mixed ancestry farm workers. The incidence of FAS in this region exceeds 60 cases per 1000 individuals.

Table II-1. Prevalence of FASD, FAS and Associated Disorders (FAE, ARND, ARBD) by Country (per 1000 cases)

Country	Fetal Alcohol Spectrum Disorders	Fetal Alcohol Syndrome
South Africa	-----	65-74*
Canada	25 – 46^	10.3^
France	6.0 (FAS and ARBD)	1.2 – 2.9
Sweden	3.3 (FAS and ARBD)	1.7
United States	10	0.5 – 2.0

Source: Africa: Viljoen et al., 2005; Canada: Habbick et al., 1996, Williams et al., 1999, Boland et al., 1998; Sweden, France, and the United States: IOM Report, 1996.
Fetal Alcohol Spectrum Disorders include FAS, ARND, ARBD and FAE.
*Western Cape Province, Republic of South Africa
^ Among Aboriginal populations in Northern British Columbia and Yukon territory

Given that alcohol consumption is the prime factor responsible for FASD, the extent of drinking in pregnancy is an important epidemiological question. Despite a number of prevention efforts, including point of sale warning signs and bottle labeling, surveillance data indicate that 10% of pregnant women drink some alcohol and 2% are binge drinking. More than 12% of women who are not using contraception and are at risk of becoming pregnant are drinking at levels that exceed 7 drinks per week or 4 or more drinks per occasion.

C. Etiology

Research has shown that, in the development of FASD, alcohol's causative effect can be influenced by a number of maternal factors, including hormone status (particularly hormones of the HPA axis), nutrition, age, parity, and years of drinking.

Research shows that genetic factors influence adverse pregnancy outcome in both humans and animal models. Animal research has also shown that the genetic

profiles of the mother and the fetus are important for determining the potential for risk of physical birth defects, prenatal mortality, learning and other neurobehavioral deficits in the offspring. In humans, the presence of a specific variant of the alcohol dehydrogenase gene, *ADH1B*2*, in either the mother or child, has been shown to decrease risk for FAS. Other studies have shown that the presence of the *ADH1B*3* variant decreases risk for neurodevelopmental deficits associated with ARBD. Both of these ADH variants have kinetic properties that make them more efficient at oxidizing alcohol to acetaldehyde, a noxious intermediate metabolite, suggesting that elevated acetaldehyde levels may contribute to decreased alcohol consumption to lessen the risk FAS and FASD.

With respect to environmental risk factors, parents' socio-economic status (SES) has been shown to be inversely associated with adverse prenatal outcomes. However, the mechanisms accounting for this finding remain to be established and the possibility exists that some factor associated with SES such as drinking pattern or nutrition may account for the observation.

Embryonic and fetal development are characterized by rapid, but well-synchronized patterns of gene expression, including epigenetic imprinting, which makes the embryo/fetus particularly vulnerable to harm from alcohol. Hence, this stage of life provides fertile ground for the gamut of teratogenic consequences. As noted in this Plan's Overview, alcohol has the ability to affect epigenetic pathways directly by disruption of metabolic events in the biosynthesis of metabolites involved in epigenetic modification (for example, the methyl donor S-adenosyl methionine) resulting in altered gene expression and consequent developmental injury. In addition, alcohol-induced errors in gene imprinting at the level of the gamete may be heritable across multiple generations. Therefore, the effect of alcohol on embryonic/fetal development is similar to shooting a moving target whereby development is differentially vulnerable at different stages of development following different durations and patterns of alcohol exposure.

Evidence for alcohol-induced alterations has been found as early as the embryonic stage of development. Research with a frog model of FASD has demonstrated that alcohol can induce developmental injury at alcohol concentrations that are attainable in heavy or binge drinking. Embryonic alcohol exposure decreased the expression of several key neural genes necessary for development (Pax6, Otx,6, Sox 3 and NCAM, TBX5, VAX2 among others). The effect of these alterations in gene expression produced outcomes consistent with the types of deficits seen in FAS including microcephaly and micro-ophthalmia as well as other ocular abnormalities, overall growth retardation, as well as delayed gut development. This research further demonstrated that reactive oxygen species (ROS) and potentially reactive nitrogen species (RNS) were involved in the mechanisms by which alcohol caused these developmental effects. The anti-oxidant ascorbic acid (vitamin C) was capable of protecting against microcephaly and overall growth impairment. Over expression of either catalase, an enzyme involved in a pathway that would reduce levels of ROS, or of peroxiredoxin 5 (PRDX5), an enzyme that reduces levels of both ROS and RNS also afforded protection from the inhibition of gut development and growth retardation, and restored the gene expression of Pax6 and other key developmental genes.

Other research studies have implicated ROS in the mechanisms by which teratogenicity develops following prenatal alcohol exposure, including programmed cell death. Programmed cell death, or apoptosis, is an essential process for normal

development. Specific cells required only at a particular stage of development undergo apoptosis once their developmental function is completed. An apoptotic event occurring either too early, or too late, can alter the developmental process. Both *in vivo* and *in vitro* studies have demonstrated that alcohol can alter cellular responses to regulatory mediators of apoptosis in susceptible cell populations. Alcohol induction of oxidative stress may cause apoptosis, in part by reducing intracellular antioxidant capacity. This increase in ROS enhances the permeability of the mitochondrial membrane which, in turn, leads to induction of an apoptotic signaling cascade involving the enzyme caspase. These findings led investigators to test whether antioxidant agents could prevent fetal alcohol injury. Results of such studies to date have been mixed, with decreased cell death in animal and tissue culture models but no change in neurobehavioral deficits observed in the offspring.

One area where prenatal alcohol exposure may bring about a life-long consequence involves the fetal programming of the hypothalamic-pituitary-adrenal axis (HPA) axis and its response to stress. Research in animal models has shown that alcohol exposure during fetal development can reprogram the HPA axis such that HPA tone is increased throughout life. The consequent sustained elevations of stress hormones can produce adverse effects on behavioral, cognitive, emotional, physiological and metabolic functions. Changes in immunological function can increase vulnerability to illnesses throughout life. While this particular research demonstrates an effect of prenatal alcohol on fetal programming of adult HPA responding, other research has demonstrated that *postnatal* maternal behaviors can permanently alter offspring through imprinting or epigenetics. In this particular study, maternal-infant interactions resulted in permanent variations in specific gene expression directly through an imprinting process. Therefore, a potential mechanism exists for epigenetic or fetal programming in the offspring of mothers exposed to alcohol during pregnancy

Another area where prenatal alcohol exposure may cause life course problems involves disturbances of circadian rhythm. Prenatal alcohol exposure has been shown to alter the circadian rhythm of developmental processes, which may contribute to long term effects on health, including sleep disturbances and psychiatric disorders.

Components of many neurotransmitter systems appear to be involved in prenatal alcohol-induced fetal injury. For example, several studies implicate the NMDA glutamate receptor system in alcohol teratogenesis. Prenatal alcohol exposure on gestational day 8 of the mouse caused an eventual change in the expression pattern of NMDA receptors, with a decrease in the NR2B receptor and an increase in the NR2A receptor. Researchers have hypothesized that this change could contribute to learning deficits in FASD as NR2A is less modifiable than NR2B. Also, the alcohol withdrawal-induced excitotoxicity of the NMDA glutamate system that follows heavy exposure to alcohol has been proposed as another mechanism by which injury to the fetal hippocampus may occur. Research has shown that the NMDA receptor blocker, MK-801, could attenuate the reductions in fetal hippocampal cell numbers in the rat associated with alcohol withdrawal. Similarly, the selective NMDA antagonist, eliprodil, was shown to reduce the severity of learning deficits in rats observed after exposure and withdrawal from alcohol, with alcohol administered on postnatal day 6 (corresponding to mid-third trimester in the human) and eliprodil administered the following day. Both of these findings indicate that glutamate/NMDA excitotoxicity can contribute to alcohol-induced fetal brain injury.

Prenatal alcohol exposure has been shown to affect the serotonergic system of the rat, inhibiting midline neural tube development. Alcohol exposure in the prenatal period has also been demonstrated to affect other neurotransmitter systems including the muscarinic acetylcholine system involved in hippocampal memory mechanisms.

Another important functional system altered by prenatal alcohol is the L1 cell adhesion system. Alcohol potently inhibits the cell adhesion and axonal growth properties of L1. Of particular interest is that children who are born with mutations involving the L1 molecule develop birth defects with a phenotype that is similar to FAS.

One striking observation is that short peptide fragments from two of the brain's neuropeptides, *activity-dependent neurotrophic factor* (ADNF) and *activity-dependent neurotrophic protein* (ADNP) have been found to afford significant protection from fetal alcohol injury at concentrations as low as the femtomolar (10^{-15}) range. Peptide fragments from ADNF and ADNP could prevent alcohol-induced alterations in the function of L1. These peptide fragments have also been found to protect against reactive oxygen injury in the developing fetus.

D. Prevention

Researchers have pursued two paths for preventing FASD. The most desirable route for prevention involves eliminating or significantly reducing alcohol consumption by women during pregnancy. Other efforts have explored the possibility of minimizing the damage caused by prenatal alcohol exposure.

The Institute of Medicine addressed the issue of prevention of FASD in the mid-1990s and proposed three approaches that differed in degree of intensity depending on the level of risk of the pregnant woman.

The broadest approach involves **universal** prevention measures targeted to the global community of men and women, and conveys general education on risks and information to abstain from alcohol in pregnancy. Examples include notices in bars, restaurants and other points of sale, broad media campaigns, and labels on alcohol beverage containers. While these efforts raise the level of overall awareness, research to date has not demonstrated that universal approaches decrease alcohol use among the group at highest risk for having an FASD child. The next level involves **selected** prevention efforts which are directed to those women who are in special risk groups, for example, a population that is known to have a greater percentage of women who drink during pregnancy, or who frequently engage in binge drinking. An example may be a screening effort in primary care or prenatal clinics in a community known to have a high prevalence of risk drinking. **Indicated** prevention is at the highest level of intensity and is directed at *individuals* known to be more vulnerable because of a high prevalence of drinking in a high risk manner, including frequent binge drinking, having a diagnosis of alcoholism, or having previously given birth to a child with an FASD. To date, the limited research on *selecte*d and *indicated* prevention efforts has shown that these methods can produce changes in drinking behavior that would be expected to decrease risk for an adverse fetal outcome. Indeed, research has shown that both screening for alcohol use and administration of brief interventions in the clinic (*selected* prevention) have positive effects on drinking reduction during pregnancy. Also, conducting a single postpartum follow-up session showed promise for maintaining the gains made possible by the

intervention during pregnancy. Several screening instruments have been demonstrated to have good sensitivity and specificity in identifying women at risk, and their effectiveness may be enhanced by computerized self-interview.

Pharmacological intervention during pregnancy is an alternative approach to prevention that may have applicability when there is early alcohol exposure before a woman recognizes that she is pregnant, or otherwise fails to stop drinking in pregnancy. Unlike many other teratogens that have a limited period of exposure vulnerability, there are many periods during gestation when alcohol can produce embryonic and fetal injury. While some agents have shown intriguing results with respect to the prevention of FASD associated injury, to date no agents have progressed to the point of consideration for human trials. Therefore, this area would best be described as at an early stage of development. However, among the promising potential agents tested in animal models are anti-oxidants that have been shown to reduce fetal cell toxicity, anti-inflammatory agents such as prostaglandin inhibitors; the nutritional co-factor choline; and agents that interfere with alcohol's action in disruption of the functioning of the L1 cell adhesion receptor. Also, two neuropeptides derived from the neurotrophic factors ADNF and ADNP have been shown to exert significant protection from alcohol-induced fetal injury in cell culture and animal models, and derivatives of these factors may offer significant potential as future preventive agents.

E. Treatment

Diagnosis: Important to the implementation of treatment is the identification of the infant or child with FAS or FASD. Diagnosis of FAS and FASD often has been difficult due to the lack of a biological marker, nonspecific and often subtle symptomatology, differences in the severity and timing of the insult, individual differences in response and resiliency, and the overall complexity and plasticity of brain development. Diagnosis in neonates and infants is further complicated because neurodevelopmental deficits important to case identification may not be discernable in infancy, and facial features may not be prominent in the neonate. Because the physical signs of FAS moderate with age, and behavioral manifestations of FASD change according to developmental stage, diagnosis during later childhood (puberty and beyond) is even more difficult than at younger ages. However, with more recent advances in the application of complex, detailed facial imaging, researchers have been using the facial dysmorphology associated with FAS as a biomarker for CNS damage following confirmed maternal gestational alcohol consumption. So, while a definitive biomarker is still lacking, the use of an objective measure, facial imaging, may confirm the use of facial dysmorphology as a biomarker for gestational alcohol exposure.

Analysis of magnetic resonance images (MRI) of the brains of adolescents and adults with FAS, FASD, and normal subjects reveals that the shape of the corpus callosum is much more variable in the brains of alcohol-affected subjects. Statistical analysis of this excess variability reveals that it can discriminate affected individuals with good sensitivity and specificity. Further, the altered shape of the corpus callosum serves as a permanent record of brain damage, even in subjects suspected of FAS or FASD relatively late in life, or who lack the physical signs of FAS. More recently, a pilot study has provided evidence for the use of ultrasound in infants, through the infant's fontanelle, in determining the shape of the corpus callosum. This approach may offer the potential to assess the corpus callosum in infants as a diagnostic indicator for FAS. Early case recognition is important in the quest for early initiative of therapy.

Therapeutics for FASD behavioral deficits: Several promising approaches to restoration or improvement of neurobehavioral deficits are being explored in animal models. Twenty days of complex motor skill training in adult rats was shown to restore performance deficits on a motor task that resulted from binge exposure to alcohol in the neonatal period. Recent results showed that this training stimulates synaptogenesis in the cerebellum. Thus, Purkinje cells that survive the initial alcohol insult are capable of experience-induced plasticity. Other forms of directed activity may have similar beneficial effects in other neuronal cell populations.

Prenatal alcohol exposure produces functional changes in the cholinergic system of the hippocampus, leading to hyperactivity, passive avoidance deficits, and impairments in spatial and working memory. Dietary supplementation with choline, a precursor of the neurotransmitter acetylcholine, was shown to decrease hyperactivity and improve spatial and working memory in young rats that had been exposed to alcohol prenatally. The choline treatment had no effect on alcohol-induced deficits in motor balance and coordination, which are controlled by the cerebellum rather than the hippocampus. Thus, choline's ameliorative effects may be selective for hippocampal dysfunction.

Of particular importance are educational and skill oriented interventions to address the learning and neurobehavioral deficits of FASD children. Pilot studies with these populations are showing improvements in performance that can enhance the life skills of individuals with FAS and other FASD.

F. Opportunities

- Apply genetic and proteomic technologies to examine alcohol's effects in altering the gene expression patterns involved in normal development, particularly with reference to systems and organs that are affected in FASD such as the central nervous system.

- Apply the technologies for the study of epigenetic modifications of DNA and histone structure to uncover alcohol's potential role in altering the normal course of gene expression, as well as the physiological and behavioral consequences of such alteration. Undertake such studies at various points in embryogenesis and fetal development that have to date been demonstrated to be particularly sensitive to the effect of prenatal administered alcohol, for example, during the development and closure of the cranial neural crest.

- Examine the interaction of alcohol with additional factors, such as maternal stress and nutritional stress in altering epigenetic patterns, and identify the sites on DNA and histone proteins where the interaction of these factors changes the genetic expression pattern.

- Continue to explore the mechanisms through which alcohol impairs the functioning of various neurotransmitter systems (glutamate, serotonin, muscarinic acetylcholine), second messenger signaling systems, and cell adhesion communication systems, in the development of fetal alcohol injury.

- Use the knowledge gained in uncovering target sites for ethanol's action on the embryogenic and fetal stages of life to begin the development of potential therapeutic or preventative interventions. In this context, focus explorations on the dietary supplements (e.g., antioxidants and choline) that are safe for use in pregnant women and identify the concomitant levels of vitamins that may be useful in pregnant women relative to those used in animal experiments for the same level of benefit. Continue to explore the potential of antagonists of alcohol's interferences with cell adhesion molecules, and of ADNF and ADNP derived peptides as potential protective agents from fetal alcohol injury in experimental model systems. It is known that choline deficiency during pregnancy does harm fetal brain development (hippocampus is one target) through decreased global methylation in fetal brain and methylation of specific genes, and in normal pregnancy, choline levels steadily increase from early gestation through parturition to account for increased need with respect to placental transfer, but to date, no studies have looked at whether alcohol causes a decrease in choline levels during pregnancy. Iron deficiency has been shown in high FAS risk populations, e.g., South Africa.

- Apply technologies arising from the NIH Roadmap program on metabolomics to the search for a metabolic profile that may serve as a marker for either risk levels of alcohol consumption, or of particular vulnerabilities for the development of FASD.

- Refine the current understanding of the neurodevelopmental signature of FAS and FASD, their relationships to and differences from other neurodevelopmental disorders such as William's syndrome. Identify indicators of these deficits at increasingly earlier ages to enable earlier interventions with FASD affected individuals. Use "self-educating' computer technologies for the analysis of 3-D facial images and MRI brain scans to identify changes in these images not recognized by the human eye. Explore the structural and functional underpinning of these alterations in deciphering targets for alcohol's teratogenesis, and to improve case recognition of FASD versus other disorders. Neurobehavioral deficits specifically associated with FASD, and those associated with other disorders, will improve the diagnosis of FASD, but can be used in the development of therapeutic interventions for both groups of affected children.

- Increase knowledge on the structural alterations in various brain regions such as the vermis, corpus callosum, hippocampus, arcuate nucleus, alone or in combination, for identification of fetal alcohol CNS deficits. Explore the potential of this knowledge to the understanding of prenatal alcohol induced functional deficits, and potential therapeutic interventions. Examine the potential for development of low to modest cost approaches for the identification of these structural deficits through prenatal ultrasound and transfontanelle ultrasound of newborns, to facilitate their adaptation into diagnostic approaches for clinical care.

- Health Services Research: Identify barriers to the implementation of alcohol screening in primary care and obstetric practice, and explore the acceptability

of new technologies in screening, such as computer assisted interviewing, and more effective integration of obstetric care with treatments for alcohol-use disorders.

- Refine approaches for selected and indicated prevention, to decrease the potential for FASD births among the women at greatest risk for these disorders.

G. Outreach

- The meetings and work of the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFAS) will continue to be supported by the NIAAA. The ICCFAS is developing a strategic plan with actions that involve the participation of alcohol researchers and research administrators. Over the next five years relevant research results will be transferred to practice. Research to Practice Meetings on Prevention, Treatment, Educating Affected Children and FASD and Criminal Justice will be co-sponsored with ICCFAS organizations. NIAAA will continue to work with SAMHSA on the development of guidelines and training materials for criminal justice personnel.

- The Health Resources and Services Administration (HRSA), a member organization of the ICCFAS, has provided funding to the National Organization on Fetal Alcohol Syndrome (NOFAS) to work with maternal care programs and gain the inclusion of alcohol screening. NIAAA will be involved in providing advice and guidance for this effort. The opportunity exists to partner with NOFAS and with HRSA to work within an ongoing program to identify research-based intervention that can be implemented in a cost effective manner in health care facilities. NIAAA will work with the HRSA Network and SAMHSA to improve the chances that alcohol screening will be selected for implementation beyond maternal care.

- NICHD, NCI, NIAAA, and NCCAM are sponsoring an initiative for a multi-center international research network designed to perform randomized clinical trials of interventions to reduce the major risks to maternal, neonatal, infant and early childhood health in resource-poor countries. An infrastructure necessary to initiate, implement and evaluate recommended interventions has developed. Alcohol abuse in childbearing age women can result in an increase in fetal damage, spousal abuse, injury, sex-related infectious diseases, and failure to support the health care of the child. NIAAA seeks to include alcohol screening and interventions in the health care of women in prenatal care and the screening of children from birth through early childhood for the disabilities that result from prenatal exposure to alcohol. NIAAA will work with the network to develop an acceptable protocol to accomplish these objectives.

CHAPTER III. Youth/Adolescence

A. Definition of Youth and Adolescence

Adolescence is a period of life characterized by dramatic changes in biological processes, as well as physical and social contexts. For the purpose of this document, we define the age range of adolescence as spanning the period between 12-17 years old. There are many factors that impinge on the development of the individual as they progress through the adolescent period. Biological changes include substantial physical growth, endocrine changes, and brain maturation that continue into the third decade of life. Important psychosocial changes include spending more time with peers and less time with family, a change in the level and type or supervision (parental or otherwise), the development of sexuality and romantic interests, and increasing independence and self-reliance. At the same time, the environments with which youth interact - schools, peers, parents and family, neighborhoods and the larger society– are changing as are the multiple ways in which youth interface with and relate to these environments. As youth traverse this complex period of life, they are expected to successfully negotiate important transitions (such as from elementary to middle school and from middle school to high school), take on new roles (such as employee), master new tasks (such as driving), develop increased self-regulation, and set long-term goals. During this time the majority of youth begin to drink (80% by the end of high school), and some experience significant alcohol-related problems including the development of alcohol use disorders.

The beginning of adolescence is demarcated biologically with the onset of puberty, and, by convention, is understood to end when an individual assumes adult roles and responsibilities. Puberty was once thought to be initiated by hormonal events triggered by neuroendocrine changes in the brain. Furthermore, puberty is not a single entity, but consists of many biological processes that may not occur at the same time, and do not necessarily progress at the same pace or have the same pattern of unfolding. As already mentioned the brain itself continues to mature during adolescence and into the mid 20s with early adolescence marked by proliferation of neurons and connections between neurons and later adolescence characterized by pruning of neural connections and increased myelination. Very important to understanding alcohol use by youth from a developmental perspective is the fact that, over the past 100 years, the endocrine changes associated with puberty have been occurring at younger ages, while the attainment of adult roles such as starting a career, finding a partner, owning a home and becoming a parent are occurring much later. The result is the dramatic expansion of the period referred to as adolescence.

Adolescents are the healthiest cohort in the population in terms of organic disease but, at the same time, they experience relatively high rates of mortality and morbidity due to their behavior, including the use of alcohol. Across many species including humans, adolescence is a time of heightened risk-taking and for many young people in our society, some of that risk-taking involves alcohol use. Further, adolescence is a period of increasing socialization often involving alcohol. For some, the increased social demands of adolescence may be accompanied by increased anxiety heightening the risk for alcohol use. In this way, alcohol use has become intertwined with the normal developmental processes of adolescence. And alcohol use both affects development and is affected by developmental processes. Therefore, an overarching developmental framework will provide a useful vantage point for advancing our understanding of underage drinking.

Early to Middle Childhood: The Period of Emerging Risk

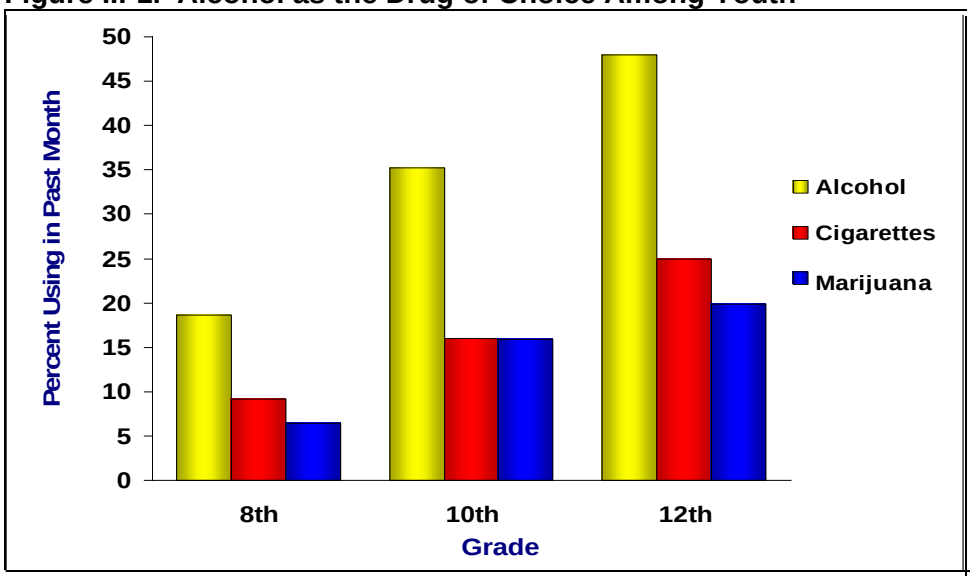
The period of time between 0-10 years involves a dynamic interplay among biological, psychological, and social factors, which overlaps with a period of tremendous physical and neuronal development. During this period, children develop critical skills and behaviors, such as problem solving, communication, and responding to the environment, at the same time as their own world of interactions expands with substantial increases in interpersonal and environmental exchanges. All of this interplay shapes normal development, as well as risk and resilience for abnormal development; the risk and resilience achieved during the period between 0-10 years manifest as pathways during later development in response to specific and nonspecific factors.

Opportunity – Apply the various data collection strategies with state-of-the-art technologies in genomics, imaging and statistical modeling to determine the relative contribution of biology, environment, and genetics to the risk for alcohol dependence or abusive alcohol consumption in later life.

B. Epidemiology

Alcohol is the drug of choice among youth, used by far more young people than cigarettes, marijuana, or illicit drugs (see Figure III-1)

Figure III-1. Alcohol as the Drug of Choice Among Youth



Source: SAMHSA 2002 National Survey on Drug Use and Health (NSDUH) data

As a result, underage drinking is a leading public health problem in this country, as young people create problems for themselves, for people around them, and for society as a whole by drinking *too much, too often*, at too early an age. A number of studies have found that early initiation of alcohol use (usually defined as starting to drink at age 13 or younger) is a risk factor for escalation of alcohol use in adolescence, and that both are risk factors for the development of alcohol-related problems in adulthood.

Nationwide surveys indicate that adolescent males and females between the ages of 12 and 17 have similar patterns of alcohol use (frequency and quantity) as well as prevalence of DSM-IV alcohol abuse and dependence. By late puberty, however, sex specific patterns and prevalence begin to diverge, with females exhibiting fewer drinking days in the past month, fewer episodes of heavy drinking, and lower prevalence of alcohol abuse and dependence.

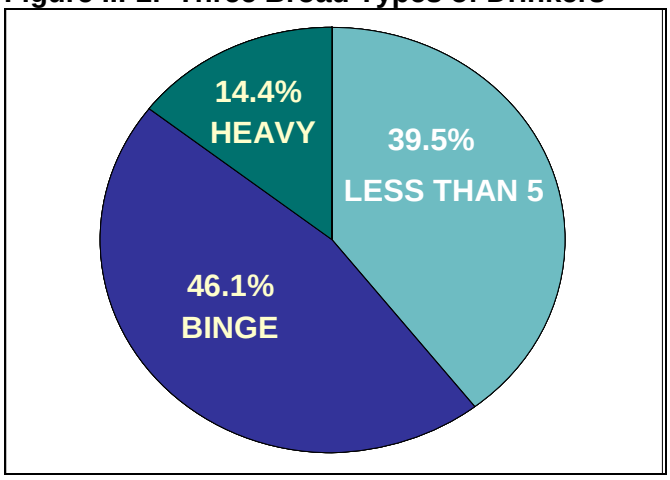
Research also suggests that early puberty, particularly in girls, is associated with higher rates of substance use and abuse (including alcohol) independent of age and school grade. The usual interpretation of this finding is that social factors and environmental stressors mediate the relationship between maturational changes during puberty and the onset of alcohol/substance use. However, hormonal mechanisms that could explain the progression of sex differences in alcohol drinking patterns during puberty, such as activation of reproductive hormones, stress responses, and their effects on brain developmental processes, remain relatively unexplored.

Even though this chapter focuses on youth from ages 12-17 and their alcohol consumption and consequences, it is important to note that alcohol is a leading cause of death for people under age 21. Each year, approximately 5,000 persons under the age of 21 die from causes related to underage drinking. These deaths include about 1,500 homicides and 300 suicides. Alcohol is also often associated with unintentional burns, falls, drownings, and other fatal and non-fatal events, and is a frequent factor in physical and sexual assault and in unwanted/unintended sexual activity. Underage drinking also causes second-hand consequences. Half of all persons who die in traffic crashes involving drinking drivers under age 21are persons other than the drinking driver. Among college students under age 21 alone, 50,000 experience alcohol-related date rape, and 43,000 are injured by another student who has been drinking.

While the prevalence of drinking among youth has decreased since the 1970s, available information from a number of national surveys indicates that rates of consumption have remained stable, at quite high levels, during the past decade.

Particularly worrisome among adolescents is the high prevalence of binge drinking. In fact, the majority of youth who drink are binge drinkers. In the figure, below, heavy drinkers are those who binge drink five times a month or more, so among youth who drink, 60.5% binge drink (see Figure III-2).

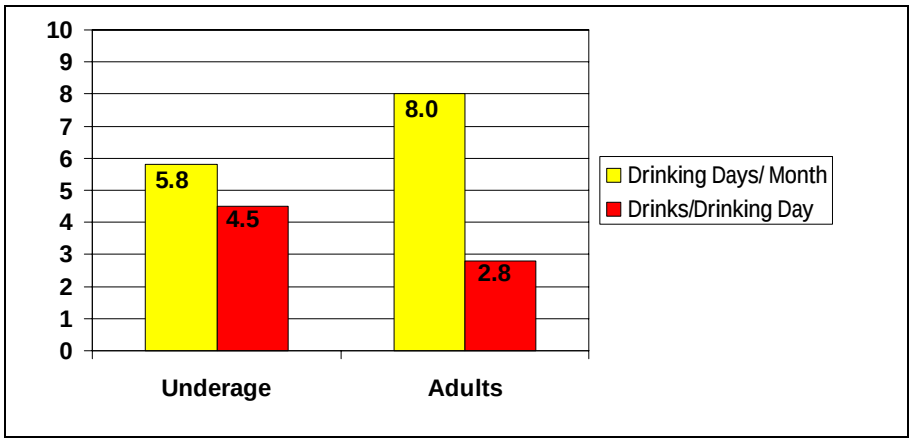
Figure III-2. Three Broad Types of Drinkers



Source: SAMHSA 2002 NSDUH data. Data based on responses to questions about drinking within the past 30 days from 4.37 million adolescents ages 12-17.

Underage drinkers consume, on average, 4 to 5 drinks per occasion about 5 times a month. By comparison, drinkers age 26 and older consume 2 to 3 drinks per occasion, about 9 times a month (see Figure III-3).

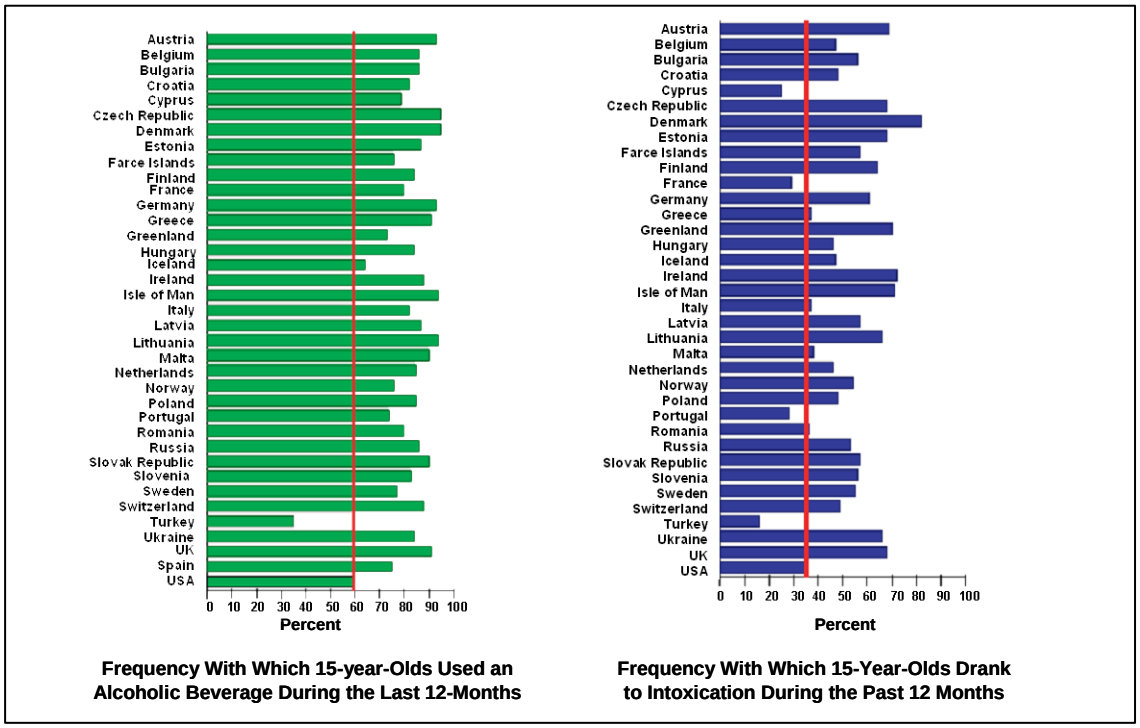
Figure III-3. Frequency vs. Quantity of Alcohol Consumption in Youth



Source: SAMHSA 2000 National Household Survey on Drug Abuse (NHSDA)

The U.S is not unique with regard to the problem of underage drinking. Alcohol use and misuse by youth is an international phenomenon (see Figure III-4).

Figure III-4. Frequency of Alcohol Use and Drinking to Intoxication During Past 12 Months in Youth Across Nations



Source: The European School Survey Project on Alcohol and Other Drugs, 2003 (http://www.espad.org/) (thick vertical bar represents the percent of 15 year olds performing that action in the United States)

C. Biology

Adolescence is a period of rapid growth and physical change; a central question is whether consuming alcohol during this stage can alter development in ways that have long-term consequences. As noted above, brain development and maturation continue during adolescence, and even into the mid 20s. Limited research with animals and humans suggests that alcohol may perturb normal brain development in adolescence and young adulthood, thereby altering neurophysiology and associated behavioral functioning.

Imaging studies have shown that the hippocampus, a brain region that plays an important role in learning and memory, is smaller in adolescents who begin drinking at an earlier age than in those who begin drinking later. Researchers have found that memory problems are common among adolescents in treatment for alcohol withdrawal. Since so many youth use alcohol on a regular basis, and often in a "binge" pattern of consumption, we must understand more about the impact of alcohol on the physiological, neurophysiological and functional development of the brain. In general adolescents are less sensitive to the acute, negative effects of alcohol, such as sedation and motor impairment, which would normally serve to limit alcohol consumption. This may partially explain the heavy, binge-like pattern of drinking undertaken by adolescents. However, on tasks with which youth are unfamiliar or less experienced, such as driving a motor vehicle, they are more susceptible to the negative effects of alcohol. The heavy, binge pattern of alcohol consumption places adolescents in repeated exposures to, and withdrawals from, the high (medically damaging) concentrations of alcohol that are thought to make individuals more vulnerable to alcohol's detrimental and toxic effects. Although withdrawal symptoms normally associated with abstinence from alcohol abuse are rare in adolescents, subsyndromal effects from binge-like alcohol exposure may still initiate harmful consequences.

D. Prevention

Prevention of alcohol problems in adolescents poses special challenges due to the unique physical, psychological, and social maturation processes occurring during this period. As the developing adolescent advances through middle/junior high and high school, and becomes active in sports and other after-school activities, he or she will likely be granted more freedom of movement and use of discretionary time, and have access to resources like money and a motor vehicle. As greater degrees of independence are obtained, the adolescent becomes exposed in a greater degree to the influences of the larger culture, including significant peer pressure, which becomes increasingly important in shaping attitudes, beliefs and tastes in clothing, music, and behavior. These intense pressures on the adolescent, in combination with their developing attitudes and beliefs, make them "moving targets" for intervention and treatment. These external influences may, or may not, be in synchrony with the competencies, interests, and capacities of any particular adolescent. In tandem with these biological and environmental changes, progressive demands are made on the developing youth for academic progress, self-regulation, and self-governance, in the face of increasing freedom to choose one's own day-to-day and life directions. Recent studies point to developmental processes intrinsic to adolescence that may support or even encourage alcohol use, abuse, and dependence. The challenge is then to reduce underage drinking despite strong psychosocial influences that may lead young people toward alcohol use since long–term consequences may result from alcohol exposure during this time of accelerated neural, endocrine, behavioral and social maturation.

Current prevention efforts approach the issue of youth drinking in two ways. *Environmental-level interventions* seek to reduce the availability of alcohol to youth and

opportunities to drink, increase penalties for violation of minimum legal drinking age laws, and reduce community tolerance for alcohol use by youth. *Individual-level interventions* seek to change knowledge, attitudes, and skills so that youth are better able to resist influences that support drinking.

At the environmental level, the most comprehensive interventions to date encompass coordinated school, family, and community programs. One such universal prevention program, implemented in the last decade called Project Northland, included school curricula, peer leadership, parental involvement programs, and communitywide efforts to address community norms and alcohol availability. The intervention was delivered to a single cohort from grades 6 through 12. Comparisons in such measures as "tendency to use alcohol" and drinking five or more drinks in a row revealed differences between intervention and comparison communities.

At the individual level, the ability of parents to influence whether their children drink is well documented and is consistent across racial/ethnic groups. Family interventions encourage parents to be aware of the risks from underage drinking, communicate with children, clarify expectations, set rules and consequences about alcohol use, and monitor children's activities. In addition to changing the knowledge and skills of young people, families can create an environment that reduces alcohol availability and increases the costs associated with drinking.

Another type of individual intervention uses the contact time with the medical system following an alcohol-related adverse event that represents a "teachable moment." Recent studies in pediatric and other emergency departments and with college age and other populations have indicated screening and brief interventions can reduce current drinking and related problems. For example, in a study of alcohol-involved teens in an urgent care setting, those who participated in a brief motivational interview showed significantly greater improvement as reflected in significantly lower incidence of drinking and driving, fewer alcohol-related social and legal problems, and fewer alcohol-related injuries during follow-up compared to those receiving standard care. Another study in a similar population found that those adolescents receiving a brief motivational intervention had significantly fewer drinking days per month and lower frequency of high-volume drinking compared with adolescents who received standard care.

E. Treatment

The rates of problematic drinking and serious consequences are high among adolescents, and many have problems, such as alcohol dependence, appropriate for intervention by the alcoholism treatment system. Data from the National Household Survey indicate that 1.47 million youth ages 12-17 met the criteria for alcohol dependence or alcohol abuse in 2003 (5.9% of adolescents in this age group). The same survey showed a major unmet need for alcohol treatment in this group. Only 216,000 (15%) received any type of treatment for their alcohol problem (see Table III-1).

Table III-1. Percent Youth Meeting DSM-IV Criteria for Alcohol Dependence and Seeking Treatment

	Alcohol Dependent	Seeking Treatment
Ages 12-17	5.9%	15%

Source: National Household Survey, 2003

Youth prefer easy access, low threshold approaches that accentuate strategies adolescents normally use to stop drinking and treatments that do not remove them from their primary home or academic settings. Youth perceive traditional services (e.g., alcoholism treatment programs, Alcoholics Anonymous) as less helpful than brief interventions tailored to salient adolescent concerns. Consequently, alternative formats, attention to developmental transitions, and use of social marketing are needed to more adequately address alcohol problems emerging in adolescence.

Adolescents in treatment for alcohol use disorders (AUDs) are likely to have more than one substance use disorder and may have other psychiatric co-morbidities; the success of treatment is lower with those who have multiple problems than with other subgroups of youth. To date, treatment for adolescent addiction has involved adapting adult treatments to youth. Ongoing research is testing some innovative and developmentally tailored interventions aimed at improving treatment outcomes.

Research has shown that adolescents in treatment for alcohol dependence have deficits in neural function and structure demonstrated through neuropsychological assessments and structural imaging. The question of whether the adolescent brain is more or less vulnerable than the adult brain to alcohol's acute and chronic effects remains to be determined. Recovery of function may also provide insight on whether such deficits may have been causative rather than consequential to the development of the alcohol use disorder.

The changes that occur in the endocrine systems during adolescence may significantly contribute in processes associated with the development of alcohol problems. Therefore, an important element for research investigation is to identify the relationship among reproductive hormones, stress hormones, and sex differences in alcohol use and dependence that unfolds during late puberty.

F. Opportunities

- Brain imaging and neurobehavioral correlations. Identify alcohol's effects on developing brain structures and behavioral regulatory systems. Techniques can be employed to examine specific brain structures in individuals who engage in drinking as compared to non-drinking controls, and to mark the progression of changes that occur with continued drinking behavior. Important targets for study include tasks related to executive functioning such as spatial working memory. As ongoing research identifies other tasks and areas of the brain that may be vulnerable to alcohol's effects, fMRI studies can be used to examine those domains. Data obtained from the NIH Neuroscience Blueprint and Program on Normal Brain Development will provide important reference data to guide the direction of these studies.

- In the longer term, as improvements in technology increase, more sophisticated techniques will undoubtedly allow the imaging of individual molecules or biomarkers of recovery in individual brains and brain regions. However, until those methods are perfected, specific modifications in imaging techniques, such as diffuser tensor imaging – dtMRI – should allow the visualization of specific changes associated with white matter tracts.

Furthermore, the quality of image gained by using a 3.0T MRI (rather than the 1.5T) may enhance the visibility of specific brain structures potentially affected by youth alcohol drinking or by treatment for youth alcohol consumption. Furthermore, the use of alternative measures to determine brain patterns, such as event related potentials, may gain prominence in the field with improvements in localization of specific areas that are affected by alcohol drinking. All of these incremental improvements in technique could substantially advance the field with respect to the degree of deficit and or amelioration afforded by treatment.

Correlate changes in brain structure and function with neuropsychological functioning using current and newly emerging neuropsychological tools from the NIH Normal Brain Development Project.

- Adolescent decision-making. The decision to initiate drinking, and to continue drinking are important elements in the pathway leading to alcohol-use disorders. Currently, researchers rely on data collected in surveys to provide information about factors that influence adolescents' decisions to use alcohol. Recognizing the limitations of self-report, for example that individuals may not be aware of everything that factors into their decision-making, it is important to utilize multiple methodologies to assess decision-making about alcohol use.

  Research in this area needs to be pursued through the expansion of investigations on the adolescent decisional process overall, and the influence of affect, external environmental factors, and expectations on those decisions. Important in the context of alcohol use is the observation that alcohol is typically used in a social rather than an individual context, by both adolescents and adults (with the exception of those who have become physically dependent on alcohol). Examining the interplay of environment, and biological traits related to temperament, and socialization, through longitudinal research and clinical study, is a direction that may uncover important factors in decisional processes about alcohol. These human studies can employ the use of time-line follow backs as one tool to assess decisional changes.

  Some of the needed decision making investigations can be carried out in laboratory simulated environments similar to those used in other human decision making research. In addition, animal research, particularly in primates, can be used to examine decisional processes related to alcohol. Through such investigations, it may also be possible to understand how alcohol affects the valence of the various factors that contribute to decision making in adolescence and whether those effects are different for adolescents than they are for adults.

- Diagnosis of and screening for adolescent alcohol problems. In order to intervene with high risk adolescent drinkers and adolescents who have alcohol-use disorders, the target individuals must be identified in a clinical or other setting. Proper identification requires diagnostic instruments that are highly sensitive and specific. While the definitions of alcohol abuse and dependence currently in use are the same for youth and adults, these two periods of the lifespan are quite different. As such, the current criteria which were developed to identify adults with alcohol disorders may not have the same diagnostic value for adolescents. An important objective is the development of diagnostic criteria for alcohol use disorders that take the special characteristics of adolescents into account.

Epidemiological assessment of existing and newly derived data offers opportunities for the development of such criteria. Adolescent specific criteria may then be used to develop screening instruments that more accurately identify high-risk adolescent drinkers and adolescents who are dependent on alcohol. Youth in both groups are appropriate targets for intervention and/or treatment. The predictive utility of adolescent diagnostic criteria and screening instruments can be tested in real world settings.

- Health Services. Similarly, once youth and adolescents are identified as high-risk drinkers or alcohol dependent, access to health services in support of their alcohol treatment suffers from barriers to service including, insurance coverage, provider-training, provider-time, and issues of confidentiality between parents and children. This lack of understanding with respect to the barriers to treatment of youth for alcohol use disorders may contribute to the under-identification or under-recognition of high-risk drinking in youth.

- Define and study alcohol behavioral markers (endophenotypes and intermediate phenotypes) for problem alcohol use by youth. An important goal is to identify very early markers for drinking risk and to determine if the relationships between these markers and problem alcohol use are correlative or causal. Of potential interest are relationships between externalizing disorders, internalizing disorders, and prenatal alcohol exposure (as discussed in the fetal section), and the development of alcohol problems. Identifying factors that play into vulnerability for very early initiation can help to identify high-risk populations that may benefit from targeted early interventions. The identification of these endophenotypes requires longitudinal study of youth as they develop through adolescence and into young adulthood. Such longitudinal studies, particularly in high-risk children, offers the potential to dissociate brain and behavioral abnormalities that are predisposing factors for alcohol abuse and dependence from those that are the consequence of chronic alcohol exposure Longitudinal studies also offers the opportunity to identify behavioral, cognitive, and emotional processes and neurobiological mechanisms of social behavior as they related to preadolescent and adolescent drinking pathways including the development of abuse and dependence Major collaborative opportunities exist to partner with other NIH institutes in such developmental studies where multiple genetic and environmental influences may be followed in a common research population that provides a basis for the study of various developmental disorders, including alcoholism, drug abuse, psychiatric disorders, obesity and eating disorders. Efforts underway in the NIH Program on Normal Brain Development will also contribute to this effort.

- The changes that occur in the endocrine systems during adolescence may significantly contribute in processes associated with the development of alcohol problems. Therefore, an important element for research investigation is to identify the relationship among reproductive hormones, stress hormones, and sex differences in alcohol use and dependence that unfolds during late puberty. One approach to examine these relationships is through longitudinal studies of hormonal, electrophysiological and other biological factors over the course of puberty. In humans, such an effort may be undertaken in collaboration with other institutes of the NIH as part of a more global examination of the biological and behavioral changes occurring throughout adolescence. Modeling in animals, both rodents and particularly primates, could contribute to answer to answer these questions.

- Research has shown that adolescents in treatment for alcohol dependence have deficits in neural function and structure demonstrated through neuropsychological assessments and structural imaging. The question of whether the adolescent brain is more or less vulnerable than the adult brain to alcohol's acute and chronic effects can be determined through the continued assessment after successful alcoholism treatment of the recovery of neural and behavioral function in adolescents, in comparison to recovery of function in adults. Recovery of function may also provide insight on whether such deficits may have been causative rather than consequential to the development of the alcohol use disorder.

G. Outreach

- NIAAA published a monograph devoted to underage drinking and development entitled, "Alcohol Development in Youth, A Multidisciplinary Overview" (Alcohol Research and Health, Vol. 28, Number 3, 2004/2005). This monograph covered a wide range of topics as reviewed by NIAAA staff members and extramural research investigators serving on the Underage Steering Committee. Among the chapters included were: 1) *Developmental Issues in Underage Drinking Research*; 2) *The Effects of Alcohol on Physiological Processes and Biological Development; 3) Genetics, Pharmacokinetics, and Neurobiology of Adolescent Alcohol Use; 4) Psychosocial Processes and Mechanisms of Risk and Protection; 5) Environmental and Contextual Considerations; 6) Interventions for Alcohol Use and Alcohol Use Disorders in Youth.*

- NIAAA will develop a working relationship with the Department of Agriculture's 4-H and other youth programs to determine how these programs might be included in efforts to reduce underage drinking. The outcomes of pilot projects and activities will be evaluated to determine effectiveness.

- Use state-of-the-art communication strategies and techniques to increase awareness of critical alcohol and health messages, including – "Early onset of alcohol use interacts with human developmental processes to increase risk for alcohol problems throughout the lifespan."

H. Collaborations

- NIAAA is involved in a joint RFA with the National Institute on Drug Abuse and National Institute on Aging at NIH, and the Institute of Neurosciences, Mental Health and Addiction in Canada on *Social Neuroscience*. The purpose of this initiative is to stimulate research on the brain mechanisms underlying social behaviors, including social decision making, interpersonal/peer relationships, self-regulation, and emotional regulation as they relate to the development of adolescent alcohol abuse and dependence.

CHAPTER IV. Young Adult

A. Definition of Young Adult

Many factors contribute to the definition of young adult. For this purpose, the ages of 18-29 are used to delineate this period, although this time frame can be further broken down into 18-24, and 25-29. For example, the late teens and early 20s see the completion of major maturational changes to the prefrontal cortex of the brain and optimization of goal-directed behavior, yet the transition from adolescence to early adulthood is not otherwise demarcated by the kind of overt biological events that typify entry into adolescence. Rather, young adulthood entry into this life stage has come to be defined by a variety of self-directed transitions that signal an individual's burgeoning independence from parental care. The pursuit of post-secondary education, enlisting in the military, and entering the workforce are a few such milestones, which traditionally have occurred when an individual is in his or her late teens or early twenties. Other events that traditionally mark this period include assuming large financial obligations, courtship, and marriage. In the U.S, most states have adopted age 18 as the legal age of majority – the point at which individuals assume responsibility for their own actions. However, from a developmental rather than a legal perspective, emerging or young adulthood now comprises an extended period of unsettled behavior for many individuals, as age of marriage and age of career initiation in the U.S., for example, have increased relative to historic norms.

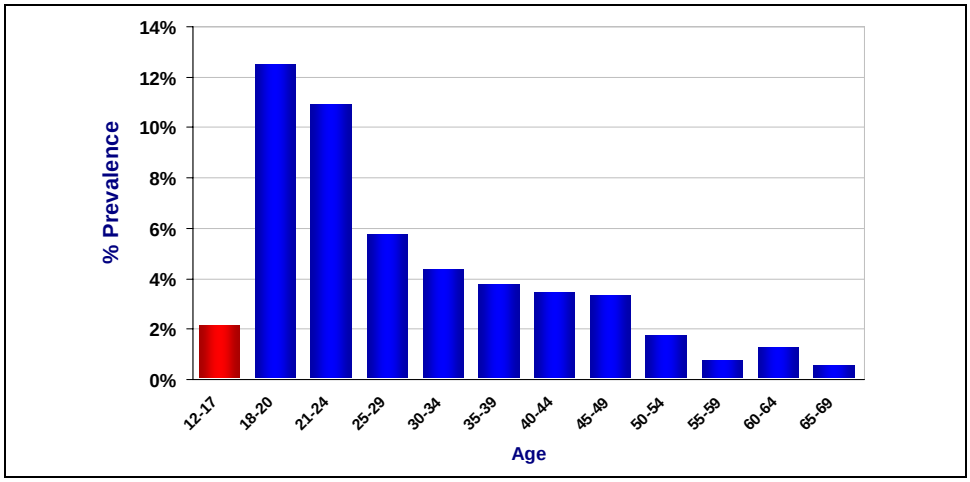
Table IV-1. Percentage of U.S. Adults 18 and Over with Past-year Alcohol Abuse or Dependence and Percentage of Those with Past-year Abuse or Dependence Who Received Alcohol Treatment, by Type of Treatment

	Past-year disorder		Type of treatment			
Age group	Abuse	Dependence	Any treatment	12-Step only	Other only	12-Step and other
18-29	7.0 (0.4)	9.2 (0.4)	5.9 (0.7)	1.3 (0.4)	2.3 (0.4)	2.3 (0.5)
18-24	6.7 (0.5)	11.6 (0.6)	6.4 (0.9)	1.4 (0.5)	2.8 (0.6)	2.2 (0.6)
25-29	7.3 (0.6)	5.7 (0.4)	4.9 (1.2)	1.0 (0.5)	1.2 (0.5)	2.7 (0.9)

Source: Adapted from Table I-8 in the Overview.

Compared to all other age groups, the prevalence of periodic heavy or high-risk drinking is greatest among young adults aged 18 to 24. Alcohol use disorders, including alcohol dependence, also peak during this period (see Table IV-1 above). While most young adults transition out of harmful drinking behaviors, a minority will continue to drink heavily into the later stages of adulthood. For example, recent NESARC data has shown that, while the prevalence of past-year DSM-IV alcohol dependence is more than 12 percent for 18-20 year olds and more than 10 percent for 21-24 year olds, by age 25-29 prevalence has dropped to less than 6 percent and is less than 4 percent for adults ages 35 and over (see Figure IV-1). These phenomena raise important research questions. For example, what factors allow some young adults to discontinue harmful drinking patterns, most often in the absence of formal alcoholism treatment? Why do others experience protracted alcohol problems well into their adulthood?

Figure IV-1. Prevalence of Past-year DSM-IV Alcohol Dependence by Age in the United States

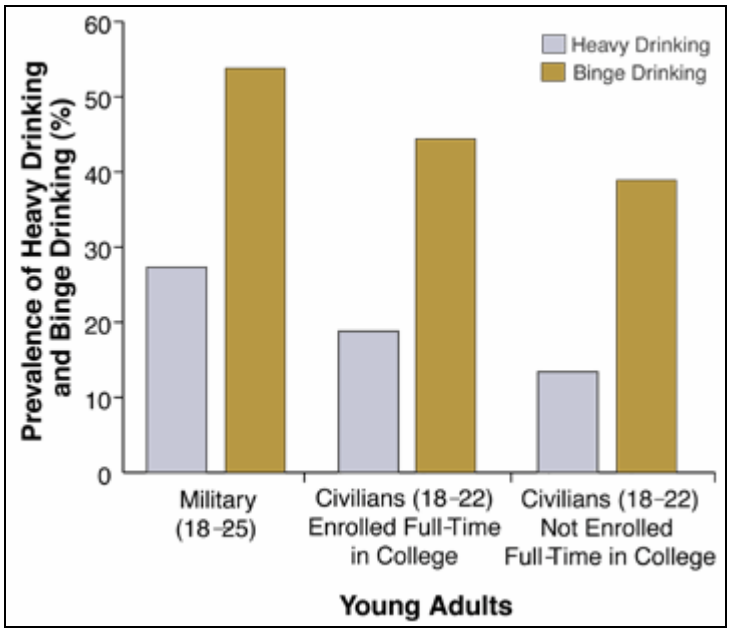


Source: NIAAA 2001-2002 NESARC data (18-60+ years of age) and SAMHSA 2003 NSDUH (12-17 years of age)

B. Epidemiology

Figure IV-2 illustrates that problematic drinking behaviors are prevalent among college, non-college, military, and civilian young adult populations. A recent review by NIAAA researchers found that from 1998 to 2001 the nationwide number of alcohol-related deaths among 18–24-year-olds rose at a rate that significantly exceeded that age group's proportional population increase. Whereas the population increased 7% from just over 26 million to almost 28 million, alcohol-related unintentional injury deaths rose 12% from 4771 to 5367. Thus, alcohol-related deaths per population of 18–24-year-olds rose 5% from 1998 to 2001.

Figure IV-2. Prevalence of Heavy and Binge Drinking in Young Adults by Specific Institution (Military, College)

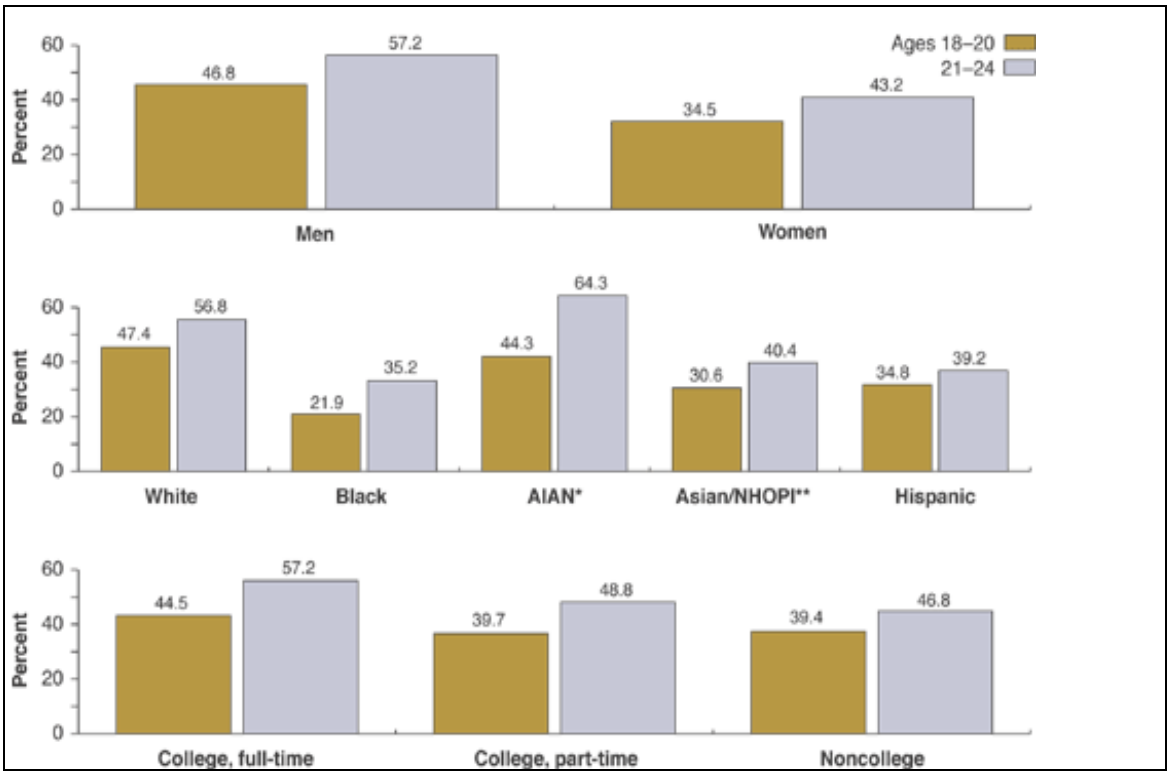


Source: Ames and Cunradi. Alcohol Use and Preventing Alcohol-Related Problems Among Young Adults in the Military Alcohol Res Health 28: 252-257, 2005. (Military data: Bray, et al., 2003; Civilian data: SAMHSA 2002 NSDUH)

According to NESARC data, in 2001–2002 over three-quarters of young adults ages 21–24 were current drinkers, as were nearly two-thirds of those ages 18–20, despite the fact that the legal drinking age is 21. More than half of young adult men exceeded the recommended daily drinking limit, as did two-fifths of young adult women (see Figure IV-3). Although the prevalence of exceeding the daily limit is higher for those ages 21–24 than for those ages 18–20, it also is substantial for those ages 18–20. Because drinking more than the recommended per-occasion maximum is likely to impair mental and physical performance, the increase over the past decade in the prevalence among young adults of drinking five or more drinks 12 or more times per year may help explain the increased risk of injury and other acute negative consequences commonly observed among college students ages 18–24.

Of the various sub-populations of young adults, college students have received perhaps the greatest research scrutiny regarding alcohol consumption in recent years. As we have learned much about alcohol use in the transitional roles through college, there is a need to expand our knowledge on the similarities and differences that occur among the young adults who enter the military or the workforce. We must also continue to explore similarities and differences in drinking behaviors of young adults from different racial and ethnic sub-populations.

Figure IV-3. Percentage of Individuals Exceeding the Daily Drinking Limit for Ages 18–20 and 21–24, by Gender, Race-Ethnicity, and College Enrollment Status



Source: NIAAA 2001-2002 NESARC data. AIAN = American Indian/Alaska Native, ** NHOPI = Native Hawaiian/Other Pacific Islander

College

Research on the college-attending population has shown that some 1,700 college students between the ages of 18 and 24 die every year as a result of hazardous drinking. In addition, nearly 600,000 college students suffer unintentional injuries under the influence of alcohol, and another 700,000 are assaulted by fellow drinking students. Alcohol-related assaults include nearly 100,000 sexually assaults or date rapes.

The proportion of college students who drink varies with where they live. Drinking rates are highest in fraternities and sororities followed by on-campus housing (e.g., dormitories, residence halls). Students who live independently off-site (e.g., in apartments) drink less, while commuting students who live with their families drink the least.

Although the existing literature on the influence of collegiate environmental factors on student drinking is limited, a number of environmental influences working in concert with other factors may affect students' alcohol consumption. Colleges and universities where excessive alcohol use is more likely to occur include schools where Greek systems dominate (i.e., fraternities, sororities), schools where athletic teams are prominent, and schools located in the Northeast.

Some first-year students who live on campus may be at particular risk for alcohol misuse. During their high school years, those who go on to college tend to drink less than their noncollege-bound peers. But during the first few years following high school,

the heavy drinking rates of college students surpass those of their noncollege peers, and this rapid increase in heavy drinking over a relatively short period of time can contribute to problems with alcohol and with the college transition in general.

Military and Non-College Civilians

Researchers have noted that heavy drinking is common among those who enlist in the military. A study that tracked high school students into adulthood found that those who entered the military were more likely than other young adults to have been heavy drinkers in high school.

A 2002 survey by the Department of Defense found that, among the 193,000 active duty military personnel between the ages of 17 and 20, 26 percent are heavy drinkers who consume five or more drinks per drinking occasion at least once a week. As shown in the table below (Table IV-2), a comparison of data from military and civilian surveys found that rates of heavy drinking among 18- to 25-year-olds in the military are higher than for civilians of the same age (32 percent vs. 18 percent for men and 8 percent vs. 5 percent for women).

Table IV-2. Standardized Comparisons of the Prevalence of Heavy Alcohol Use[a] Among 18- to 25-Year-Old Military Personnel and Civilians, Past 30 Days, by Gender, 2001–2002

	Comparison Population	
Gender	**Civilian**	**Total DOD**
Males	17.8% (0.5)	32.2% (2.3)[b]
Females	5.5% (0.3)	8.1% (1.0)[b]
In Total Population	15.3% (0.4)	27.3% (2.1)[b]

Source: Ames and Cunradi. Alcohol Use and Preventing Alcohol-Related Problems Among Young Adults in the Military Alcohol Res Health 28: 252-257, 2005. (Military data: Bray, et al., 2003; Civilian data: SAMHSA 2003 NSDUH)

NOTE: Table entries are percentages, with standard errors in parentheses. Civilian data have been standardized to the U.S.-based military data by gender, age, education, race/ethnicity, and marital status. Data for the total Department of Defense and the individual services are U.S.-based population estimates (including personnel in Alaska and Hawaii).

[a] Defined as consumption of five or more drinks on the same occasion at least once a week in the past 30 days.

[b] Significantly different from the civilian estimate at the 95-percent confidence interval.

C. Biology

Research in college students has found short-term health-related consequences of heavy drinking such as hangovers, nausea and vomiting are experienced by a large minority, if not the majority, of such students. One survey of students at 89 schools across the nation produced a self-report result of 40% with at least one hangover (47% of drinkers) and 47% (56% of drinkers) having nausea or vomiting as a result of alcohol or other drug use within the year. In one study at a New England university where almost all students (97%) drank alcohol within the year, 29% of the student sample reported that anywhere from one-half to 24 hours of their normal functioning were lost "in recovery" from drinking in the last week. Alcohol poisoning, alcohol-induced coma, and the fatal outcomes resulting from extremely high blood alcohol levels induced by excessive alcohol consumption are occasional, but not unfamiliar incidents in campus health centers and local hospital emergency rooms, although systematically collected data on the prevalence of student alcohol poisoning are not available in the research literature.

Longer term consequences of heavy alcohol use to one's health may include reduced resistance to illnesses. Self-reported illnesses were correlated with drinks consumed per week among undergraduates enrolled in a general education course at a large mid-western university. Although light to moderate consumption was not significantly associated with increased health risks, consuming an average of 22 drinks or more per week was associated with increased upper respiratory infections, and consuming 28 drinks or more was associated with greater acute illness on an aggregate measure, thus suggesting that heavy alcohol consumption contributes to lowered resistance to common illnesses among students.

With respect to young adults in the military, one study found that the highest levels of negative effects—serious consequences (e.g., missing a week or more of duty because of a drinking-related illness or being arrested for driving while impaired), productivity loss, and dependence symptoms—occurred among military personnel in the lowest pay grades. Other serious consequences included not being promoted, receiving a low performance rating, being arrested for another alcohol-related reason, being involved in a traffic crash resulting in injury or property damage, and fighting while drinking. These pay grades generally correspond to the youngest enlisted service members, who typically lack a college education. During 2002, 20.2 percent of junior enlisted personnel reported serious alcohol-related consequences, 27.2 percent reported lost productivity, and 22.6 percent reported symptoms of dependence.

D. Prevention and Treatment

Researchers have noted that young adults rarely identify themselves as problem drinkers, suggesting that proactive screening approaches may be necessary to identify problem drinkers in young adult populations.

With respect to college populations, a 2002 review of college drinking prevention strategies found that campuses would best serve the student population by implementing brief, motivational or skills-based interventions, targeting high-risk students

identified either through brief screening in health care centers or other campus settings or through membership in an identified risk group (e.g., freshmen, Greek organization members, athletes, mandated students). More recently, researchers have analyzed the effects of interventions on college students. In an examination of a multi-site environmental prevention initiative, investigators reported significant although small improvements in alcohol consumption and related harms at colleges that most closely implemented a particular program model. Other investigators found that environmental DUI campaigns similar to those validated in community prevention trials can be effective in college settings, but noted that further research is needed to determine the robustness of the changes associated with such campaigns. The issue of determining effective strategies for identifying, recruiting and retaining students in efficacious individually focused prevention services remains, as is the determination of the effectiveness of mandated student prevention services.

With respect to young adult military populations, current strategies to prevent alcohol problems include instituting and enforcing policies that regulate alcohol availability and pricing, deglamorizing alcohol use, and promoting personal responsibility and good health. The U.S. military has implemented policies and programs designed to reduce alcohol use and related problems among personnel. However, there has been little formal evaluation of these programs.

Several studies indicate that the non-student population of emerging adults is an important target for preventive interventions, especially because people in this segment of the population may be less likely to mature out of heavy drinking patterns established during adolescence. Although the non-students' risks for alcohol-related problems in their early twenties may not be as high as those of students' recent research has shown that the risk for alcohol-related problems in non-student young adults is steadily increasing towards those of college students. Unlike students, however, the risks for non-students appear to increase over time. This population does not have the benefits of campus health care centers or institutionally based programs that college students have. Similarly, students who do not live on campus may not have the benefits of campus alcohol prevention programs (which often are designed for residents) or the protective benefits of campus organizations and peer groups. Furthermore, in addition to limited exposure to alcohol-related services, the non-student/non-military population of individuals may not have exposure to mental health services that are available to the individuals in a structured setting such as college or the military. The lack of access to mental health care or health care in general may predispose these individuals to comorbidities associated with excessive alcohol consumption.

E. Opportunities

- Intervening with emerging adults as they make the transition out of high school will ensure that interventions reach people who would not otherwise receive them. The period following high school graduation is an ideal time for interventions intended to prevent the problems that may result from such escalations in use, given that alcohol use increases and specific patterns of alcohol use change considerably around this time. Furthermore, non-college bound individuals are not likely to be exposed to campus-wide alcohol education programs and subsequent interventions, thus their risk for early onset of problem drinking may be higher than college-bound individuals. Because most of the research on drinking among emerging adults has

focused on college students, an increased understanding of non-student populations can now be obtained to better inform the design of appropriate prevention efforts.

- Apply new technologies in neuroscience research to further understand how young adults with alcohol use disorders differ from other age groups in terms of brain functions linked to alcoholism. Since the physically debilitating effects of alcohol-induced organ damage are rarely expressed in this age group, it would be important to determine if the brain, also a target of the toxic effects of alcohol, shows signs of alcohol-induced injury earlier than other organs, and, in those young adults who stop drinking, whether the brain shows a return to baseline level of function. Using objective measures of brain function such as EEG, ERP and specific brain imaging techniques (e.g., diffusion tensor imaging) to identify neural changes that will provide direction with respect to why young adults may increase their drinking during this particular period of time, and how their brains differ from, for example, young adults who just began drinking versus those who stopped drinking after adolescence. Once these biological changes are documented, the benefits of individualized therapies for intervention may be developed.

F. Outreach

- Audience segmentation research conducted at NIAAA has revealed that urban-dwelling young adults comprise a major segment of U.S. society that binge drinks two or more times a month. Thus, binge drinking young urban adults are a well-delineated group of individuals at significant risk for alcohol-related problems. This research has also revealed their primary cities of residence, their beliefs, social norms, their mass media viewing habits, their shopping habits, food preferences, health habits and typical sports and leisure activities. Thus, we have rich descriptive data about the lives and habits of binge drinking young adults. This information can provide a strong and unique foundation for programmatic prevention intervention research for these at-risk young adults.

- Government entities such as Office of Juvenile Justice and Delinquency Prevention (OJJDP), National Highway Traffic Safety Association (NHTSA), and the military share an interest with NIAAA and SAMHSA in reducing underage drinking and its consequences. NIAAA collaborated with OJJDP in evaluating its initiative to address underage drinking in rural communities and plans to work with OJJDP and the Air Force to evaluate an Air Force Base – Community Partnership to reduce drinking among servicemen under age 21. NHTSA continues to participate in the NIAAA programs to reduce underage drinking in college students. Opportunities exist to increase interactions and partnerships with the Department of Defense agencies involving collaborations with OJJDP and NHTSA.

- A collaborative alcohol research planning grant at the University of Hawaii is one example of NIAAA attempts to include underrepresented Asian Americans and Pacific Islanders in our programs, as researchers and as

study participants. The Institute is working with the National Association of Asian and Pacific Island Families Against Substance Abuse (NAPAFASA) to develop culturally and language appropriate information on alcohol use and abuse and health. The Institute supports an Alcohol Research Center in California with a researcher of Asian heritage as the principal investigator. This Center will be active in promoting outreach and research activities relevant to the Asian community.

- The Institute has long supported research at Hispanic Serving Institutions. The objective is to use the Spanish translations of publications and the research capacity developed in these institutions to improve alcohol prevention and treatment strategies in the Latino community. NIAAA program administrators are actively involved with the NIDA Latino Research Initiative.

- NIAAA will explore opportunities to work with a new CDC Center of Excellence in Health Marketing and Health Communications at the University of Connecticut. The University of Connecticut Center includes efforts to reduce drug and alcohol use among youth and young adults.

- NIAAA will update/re-issue college drinking report in 2007.

- NIAAA will use college drinking process/materials as a template for developing and disseminating essential alcohol messages and materials for the gamut of lifespan stages.

CHAPTER V. Midlife

A. Definition of Midlife and Epidemiology

While some may view the underage and young adult life stages as perhaps the most problematic periods for alcohol abuse and dependence, a much more complete spectrum of alcohol-related problems and issues becomes manifested during the adult period of life often referred to as mid-life. At midlife, many of the pathological consequences of heavy alcohol use become most evident, and individuals with alcohol dependence are most likely to seek treatment of their alcoholism at this time.

As with young adulthood, entry into midlife is not signaled by specific biological events. But unlike young adulthood, there is no legal construct analogous to the "age of majority" associated with midlife. Typically, a person in mid-life has assumed one or more "stable" responsibilities of career, marriage, and family life. Chronologically, this period may be viewed as encompassing the 30-59 year old age, but these boundaries are not exact and will vary among different individuals. Table V-1 shows that percentage of individuals in their midlife meeting criteria for alcohol dependence or alcohol abuse within the past year, at 3 and 5 percent, respectively, and that the percent of those individuals receiving any type of treatment during their lifetime for their alcohol use disorder is only 8.5 percent.

Table V-1. Percentage of U.S. Adults 18 and Over with Past-year Alcohol Abuse or Dependence and Percentage of Those with Past-year Abuse or Dependence Who Received Alcohol Treatment, by Type of Treatment

	Past-year disorder		Type of treatment			
Age group	Abuse	Dependence	Any treatment	12-Step only	Other only	12-Step and other
30-59	5.0 (0.2)	3.0 (0.2)	8.5 (0.7)	0.8 (0.2)	3.1 (0.5)	4.5 (0.6)
30-44	6.0 (0.3)	3.8 (0.2)	8.9 (1.0)	0.7 (0.2)	3.2 (0.7)	5.0 (0.8)
45-59	3.9 (0.3)	2.0 (0.2)	7.5 (1.2)	1.0 (0.4)	3.0 (0.8)	3.5 (0.8)

Source: Adapted from Table I-8 in the overview.

B. Biology

Chronic diseases associated with alcohol abuse and alcoholism predominate among mid-life rather than any other age group. Alcohol abuse and alcohol dependence are but two of the disorders that result from the chronic heavy use of alcohol. Many other alcohol-use disorders also manifest in the mid-life stage of life, including several types of alcoholic liver disease, alcoholic pancreatitis, several types of cancer, such as esophageal, larynx, colon, and liver, disorders of the heart and vascular system including alcoholic cardiomyopathy, alcohol-related brain disorders, as well as other adverse effects upon the endocrine and immune system (see Table I-6 in the Overview Section). An alcohol attributable factor (AAF) indicates the relative significance of alcohol as a causal factor in the onset and progression of certain diseases or its role in specific types of injury. Table V-2 shows that several diseases, including cancer, have an alcohol attributable factor ranging from 25% to 75%, while the alcohol attributable factor for injuries, including those involving motorized vehicles, is just over 40%. These

data show that alcohol has a tremendous impact on the human population in a multi-faceted manner.

Table V-2. Selected Alcohol-Related Diagnoses, Alcohol-Attributable Fractions (AAFs), and Age Ranges Included in the Calculation of AAFs

ICD-9-CM Code	Diagnosis	AAF	Age
	Alcohol-Related Diagnoses With AAFs Equal to 1		
303	Alcohol dependence syndrome	1.00	15 and older
305.0	Nondependent abuse of alcohol	1.00	15 and older
425.5	Alcoholic cardiomyopathy	1.00	15 and older
571.0	Alcoholic fatty liver	1.00	15 and older
571.1	Acute alcoholic hepatitis	1.00	15 and older
571.2	Alcoholic cirrhosis of liver	1.00	15 and older
	Alcohol-Related Diseases With AAFs <1		
011, 012	Pulmonary and other respiratory tuberculosis	0.25	35 and older
140-149	Malignant neoplasm of lip, oral cavity, and pharynx	0.50	35 and older
150	Malignant neoplasm of esophagus	0.75	35 and older
151	Malignant neoplasm of stomach	0.20	35 and older
155	Malignant neoplasm of liver and intrahepatic bile ducts	0.15	35 and older
571.5	Cirrhosis of liver without mention of alcohol	0.50	35 and older
	Alcohol-Related Injuries With AAFs <1		
E810-E825	Motor vehicle traffic and nontraffic accidents	0.42	All
E960-E969	Homicide and injury purposely inflicted by other persons	0.46	15 and older

Source: Adapted from: McDonald AJ 3rd, et al. US emergency department visits for alcohol-related diseases and injuries between 1992 and 2000. Arch Intern Med 164(5):531-7, 2004

C.1. Metabolism and Organ Injury

The routes by which alcohol causes organ pathologies continues to be of great interest as an understanding of these mechanisms is key to the development of both preventive and treatment approaches to these disorders that, as noted above, exact high morbidity and mortality in the U.S. population. Alcohol may cause tissue and organ injury via many mechanisms, and researchers in recent years have gained an increased understanding of several factors contributing to the development of these conditions. But a complete understanding of the mechanisms underlying these diseases, whether they are common across multiple organs, or specific to only one organ, requires exploration and identification of new knowledge.

Alcohol by itself, or through its metabolites, can elicit various pathologic conditions. Alcohol also may serve to perturb other metabolic pathways thereby changing the relative concentrations of other biological intermediates in eliciting the development a particular pathologic condition. For example, alcohol may alter pathways involved in the biosynthesis of methyl donors, or in generating reactive oxygen species or in depleting antioxidants all of which may be detrimental to cells, tissues and organs.

One of the direct routes by which the alcohol molecule contributes to organ pathologies is through its actions on the intestinal mucosa, an action that increases the permeability of the intestine to the bacterial endotoxin lipopolysaccharides (LPS) into the circulatory system. LPS is an important factor in the development of alcoholic hepatitis, which in turn may contribute to the development of other liver pathologies such as liver cirrhosis and cancer.

The alcohol metabolite acetaldehyde also may serve as a potential source of organ cell toxicities. Acetaldehyde is the first metabolic intermediate in the oxidative metabolism of alcohol. Acetaldehyde can form adducts with various proteins and other molecules potentially disrupting their normal physiological function. Individuals with specific variants of the two major enzymes in alcohol metabolism, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) achieve elevated levels of acetaldehyde when they consume alcohol. These ADH variants are the alleles *ADH1B*2* or *ADH1B**3, and the ALDH variant is the allele *ALDH2*2*. The consequence of possessing one of these enzyme variants, especially the ALDH variant, can produce a dysphoric state that includes facial flushing and nausea. Experiencing these unpleasant reactions can limit the desire to consume alcohol. It has been shown that Individuals with the *ALDH2*2* variant have a greatly reduced risk for alcohol dependence. Most likely related to the decreased drinking, individuals with the *ALDH2*2* variant have over a 70% reduction in alcoholic cirrhosis, presumably due greatly reduced frequency and quantity of alcohol consumption. While individuals possessing both the ADH and ALDH variants are at lower risk alcohol dependence (alcoholism), when they do drink, they are likely at higher risk for tissue and organ pathology from acetaldehyde.

Another route to alcohol-induced tissue injury is through the generation of reactive oxygen species (ROS). As presented in an earlier section, the cytochrome P450s as well as the mitochondrial oxidative chain are capable of generating ROS as a consequence of alcohol metabolism. When sufficient levels of ROS are generated they can deplete the cells reserve of antioxidants, among which is glutathione, thereby increasing the likelihood of oxidative injury.

Elevated levels of ROS have been shown to lead to the peroxidation of lipids, proteins, and DNA. The products of lipid peroxidation include two aldehydes, malonedialdehyde (MDA) and 4-hydroxynonenal (HNE). As is the case with acetaldehyde, both of these aldehydes can form adducts with proteins. As well, acetaldehyde and MDA can react with proteins in a synergistic manner to generate a stable adduct, MDA-acetaldehyde-protein adduct (MAA). MAA has been demonstrated to be immunogenic and it can induce inflammation and autoimmune reactions in various systems, including the circulatory system, and alter neuroendocrine functioning.

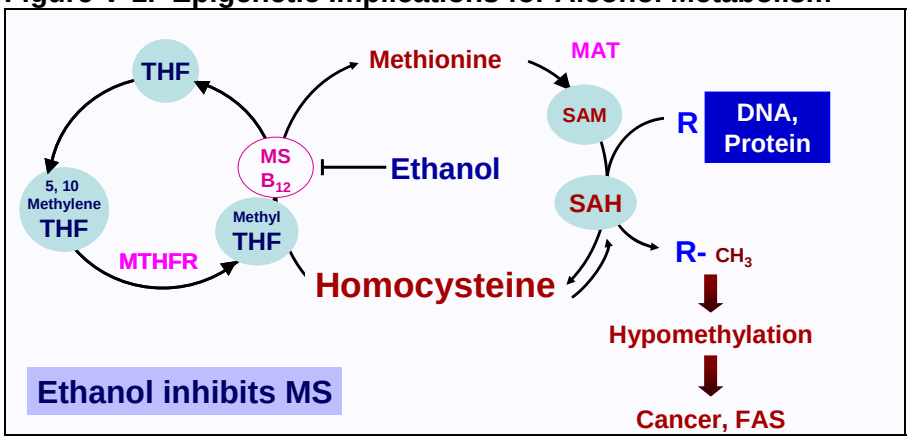
Another consequence of the elevated levels of ROS is the potential for mitochondrial damage which affects cell survival by inducing programmed cell death

(apoptosis). ROS may further cause organ injury through the alteration of gene expression. ROS are capable of stimulating transcription factors such as NFκB and AP-1, which in turn increases the genetic transcription of inflammatory cytokines (part of the disruption of mitochondrial signaling pathways) leading to tissue damage.

Fatty acid ethyl esters (FAEE) are another class of metabolic products arising from alcohol metabolism, in this case via a non-oxidative esterification between fatty acids and alcohol. FAEEs may accumulate in significant concentrations in some organs, including the pancreas where they may contribute in the development of acute and chronic alcoholic pancreatitis.

Alcohol use may also lead to the development of organ pathologies by altering the mechanisms through which normal epigenetic regulation occurs (see Figure V-1). For example, in a rat model alcohol has been shown to cause an increase in the acetylation of one particular histone protein, H3, in a site-specific manner. The consequence is an increase in transcription of a number of genes, including the gene for the rat class I ADH enzyme. This research further showed that acetate, an alcohol metabolite, was responsible for this effect by acting upon the enzyme histone aceteyltranferase (HAT).

Figure V-1. Epigenetic Implications for Alcohol Metabolism



Source: Garro et al ACER 15:395, 1991; Lu et al., Am J Physiol Gastrointest Liver Physiol 279:G178, 2000; Lu and Mato, Alcohol 35:227, 2005; Mason and Choi Alcohol 35:235, 2005.

In another example, alcohol, at high intoxicating doses, has also been demonstrated to bring about a significant reduction in tissue levels of the metabolite, S-adenosylmethionine, required for the methylation of both histones and DNA. By inhibiting the biosynthesis of methionine at the level of the enzyme methionine synthase (MS) (Figure V-1) the synthesis of the methyl donor S-adenosyl methionine will be impaired, and in turn the methylation of histones and DNA. In this manner, alcohol has the potential to cause significant disruption in gene expression altering many biological processes that may result in various disease states. Decreased DNA methylation has been linked to tumor formation, although it is not known whether this is the route by which alcohol increases the risk for the development of cancer in such organs as the liver, throat, larynx, and esophagus.

As noted in an earlier chapter, the oxidation of alcohol to acetaldehyde and subsequently to acetate is accomplished by the reduction of the co-factor nicotinamide adenine dinucleotide (NAD^+) to its *reduced* form, NADH. This changing in the oxido-reductive (redox) state itself has the potential to cause metabolic changes, including those that involve gene expression. One example of this has been demonstrated in yeast and rat studies of caloric restriction. Caloric restriction increases NAD^+ relative to NADH. The yeast enzyme histone deacetylase, Sir2, and the rat version of this enzyme, SIRT1, respond to this increase in NAD^+ by significantly increasing their catalytic activity. The function of histone deacetylase is to remove acetyl moieties from specific sites on histone proteins. In turn, the removal of the acetyl moieties silences selected genes in the region of the affected histone proteins. Among the genes silenced are those that code for enzymes involved in the deposition of lipids into fat cells, a desired effect during a period of starvation. While the shift in the NAD+/NADH ratio resulting from alcohol metabolism, which would be in the opposite direction to that arising from calorie restriction, has yet to be shown to have an effect on gene expression mechanisms, the possibility of observing this phenomenon is worthy of pursuit.

C.2. Organ Disease

Many of the major systems and organs of the body may develop a disease state from heavy and long-term use of alcohol. Several of these disorders are presented in the section on epidemiology (above). While advances in our understanding of all of the diseases are not discussed here, particular note is made of research findings on alcoholic liver disease because of its identification as the leading cause of death from alcohol.

Liver Damage. The multiple disorders of the liver that can arise from alcohol use are collectively referred to as *alcoholic liver disease*. Among these is fatty liver, a condition once considered to be benign. Other alcohol-derived diseases in the liver include an inflammatory disease, alcoholic hepatitis, and alcoholic cirrhosis, a disease characterized by marked scarring of the liver. Other agents, such as a variety of other chemicals and various bacterial and viral agents may also bring about liver disease, and alcohol has generally been considered to accelerate the progress of liver disease arising from viral agents such as hepatitis C, one of the other major causes of liver disease in the U.S. However, while individuals with hepatitis C who drink clearly have increased risk for progression to cirrhosis, whether there is an interactive as compared to a simple addition effect of the alcohol exposure, or whether there is a threshold dose above which alcohol accelerates viral liver diseases remains to be determined.

Alcohol-induced liver disease (ALD) occurs in only about 15-20% of heavy alcohol consumers suggesting that genetic factors may contribute to this process. Recent research has suggested that such genetic factors as the presence of mutant c2 allele of CYP2E1 may increase the risk of alcoholic liver disease.

C.3. Genetic Variants and Alcohol Pathology

Genetic factors have also been considered to underlie the risk for other alcohol-related disorders, beyond alcohol dependence itself which was discussed previously (Young Adult). Research has suggested that individuals with the *ADH1C*1* allele have an increased risk to develop breast cancer from moderate amounts of alcohol. However, a putative mechanism to explain this association has not been established. It is also possible the genetic risk factor is not *ADH1C*1* but *ADH1B*2*, a variant of ADH which is in linkage disequilibrium with *ADH1C*1*. Also, several polymorphisms of *CYP2E1* have been identified and a few preliminary studies have been undertaken to determine their effect on alcohol metabolism and tissue damage. In one study, an association between the m2/m2 *CYP1A1* genotype and alcoholic liver cirrhosis was found. Another study found a relationship involving glutathione S-transferase where the Val/Val *GSTP1* variant was associated with chronic pancreatitis.

C.4. The Effects of Moderate Alcohol

In addition to the development of pathologic conditions, many years of epidemiological studies have produced findings to suggest that moderate alcohol use (defined as no more than one drink per day for women and two drinks/day for men) may afford a degree of protection from a number of disease conditions including coronary artery disease (CAD), type 2 diabetes, dementia, and ischemic stroke. Although some mechanisms of actions have been studied more basic research offers the potential to confirm these initial findings and more fully understand the means by which protection is afforded. Such findings could guide the development of pharmaceutical approaches for the prevention and treatment of these disorders.

Of all of the disorders that may benefit from moderate alcohol consumption, CAD has been the most studied. Mechanisms that appear to underlie alcohol-induced cardioprotection include changes in serum lipids, blood clotting proteins, platelets, anti-oxidant polyphenols and inflammatory cytokines. In addition, several reports suggest that moderate alcohol consumption lowers systemic markers of inflammation, e.g., C-Reactive Protein (CRP) associated with increased risk for CHD. Also, exposure of the myocardium to a moderate alcohol dose before an ischemic insult resulted in up to an 80% reduction in cardiac damage. Enhanced recovery appears to be is associated with sustained activation of ε-Protein Kinase C (PKC).

One potential mechanism underlying alcohol-induced reduction of risk for Type II diabetes is an increase in insulin sensitivity. Formation of advanced glycation end products (AGE's) and their binding to vascular wall components contributes to atherogenesis. The anti-atherogenic effect of moderate alcohol consumption may be linked to acetaldehyde, which can react with nucleophilic precursors of AGE's to prevent AGE formation and lipoprotein oxidation.

Some research to date on the mechanisms underlying alcohol-induced reduction of risk for age-related dementia have focused on constituents of alcoholic beverages including wine such as polyphenols, tannins, and anthocyanin pigments that have antioxidant and anti-inflammatory properties.. In degenerative diseases of the brain, alterations in consciousness are associated with regional deficits in the cholinergic system. Moderate alcohol consumption has been shown to enhance the release of acetylcholine in the hippocampus which may underlie its neuroprotective effect.

A complete understanding of the biological mechanisms underlying the protective or beneficial effect of alcohol consumption may improve our understanding of the molecular targets that could lead to development of therapies for coronary artery disease, dementia and diabetes.

C.5. Alcohol and Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS)

HIV causes AIDS, which has killed more than 500,000 people in the United States since the HIV/AIDS epidemic was first recognized in 1981. As many as 950,000 people in the U.S. may be infected with HIV. The epidemic is growing most rapidly among minority populations and is a leading killer of African-American males ages 25 to 44. According to the Centers for Disease Control and Prevention (CDC), AIDS affects nearly seven times more African Americans and three times more Hispanics than whites. In recent years, an increasing number of African-American women and children are being affected by HIV/AIDS.

A substantial body of research indicates that chronic alcohol consumption may somehow make it easier for the virus to establish an infection and accelerate the disease and death of HIV-infected people who progress to AIDS. Alcohol also may interfere with the metabolism of anti-HIV medications. The reason for alcohol-facilitated disease progression is unclear but may involve basic biological effects of alcohol and its metabolites on the virus and its tissue target.

Social factors also influence the interaction between HIV and chronic alcohol consumption and may affect the progression to AIDS. People with alcohol use disorders are less likely to be tested for HIV. If they do not get tested and are positive, these individuals are less likely to contact a primary care provider regarding treatment, and are less compliant with therapeutic agents for HIV or related diseases. Excessive alcohol consumption is closely associated with HIV/AIDS risk behaviors such as unprotected sexual intercourse and intravenous experimental drug use. For whatever underlying reasons, risk-taking behaviors are more likely to occur in younger than older individuals. Although HIV is most commonly diagnosed at midlife, HIV infection usually is contracted earlier in life, typically during the young adult stage, a period often characterized by heavy alcohol consumption or binge drinking and increased prevalence of high risk behaviors associated with HIV transmission. Therefore, prevention efforts should target young people as well as individuals at midlife.

Studies estimate that more than 80 percent of HIV-infected individuals drink alcohol and that between 30 and 60 percent of people with HIV also have alcohol use disorders. Alcohol consumption has been reported to increase by more than 20 percent in individuals who are diagnosed with HIV infection, suggesting significant variation in alcohol use across the course of HIV infection and disease. People with HIV/AIDS may get life-threatening diseases called opportunistic infections, which are caused by viruses or bacteria that usually do not make healthy people sick. HIV-infected individuals may also suffer from depression, dementia, various psychiatric conditions, and early neuropathology, manifested as impaired cognition and motor function, and poor executive function. Given the range of co-morbidities and difficulty in diagnosis co-morbidities in HIV+/alcohol consuming individuals, there may be considerable impetus for following clinical cohorts in a longitudinal manner in order to understand the complexity associated with co-morbidities presented by affected individuals.

D. Treatment: Mechanisms of Behavior Change

Most individuals who seek alcoholism treatment do so during the midlife period. Currently available treatments, which include behavioral therapies and those that employ behavioral treatment with newly available medications, help many such individuals successfully recover from alcohol dependence. With minor exceptions, therapeutic approaches using different models yield similar results, and there is only minimal interaction with a wide variety of demographic and clinical patient characteristics.

Just as some young adults recover from alcoholism without the benefit of treatment, some individuals' transition away from alcoholism during midlife without the help of any specialty alcohol treatment, a phenomenon sometimes referred to as "aging out." Indeed, the NESARC and other studies reveal that a large majority of heavy drinkers (including those with dependence) reduce or stop drinking without seeking help in a specialty treatment program. However, many other individuals either do not experience this aging out phenomenon at all, or achieve multiple episodes of short-term success from their alcohol use disorder followed by relapse back into alcohol dependence.

People who resolve heavy drinking and its related problems without specialized treatment differ systematically from those who do. Recovery outside of treatment is more likely in those with fewer symptoms of dependence, less co-morbid psychiatric disorders, less pressure to quit drinking, and more social capital. This group of individuals forms a unique population for further study. Although these individuals resolve their alcohol use disorder, a more comprehensive understanding of how the natural recovery occurs would provide the research community with the information required to develop interventions targeting those individuals who would not normally seek treatments. One of the goals of this area of research would be to reduce the amount of time these individuals must endure the current and future range of consequences related to their alcohol use disorder before they age out or recover naturally. Progress has been made to delineate trajectories and their statistical predictors among young people, where much non-treatment change takes place.

Still, a better understanding of the characteristics, mediators, and environmental factors that motivate individuals to try to change their drinking behavior, either on their own or through professional alcoholism treatment, will greatly aid the search for improved prevention and treatment strategies. If specific psychotherapy techniques are not primary change agents, how does change occur? Even if "common factors" such as therapist empathy, expectancy, therapist allegiance to the model, and the therapeutic alliance are change agents, how, exactly, do they work? In addition, improving the efficacy of alcoholism treatment will require greater knowledge of the factors and mediators that underlie a transition from alcohol dependence in those individuals who are successful in recovering, in both the absence and presence of formal alcoholism treatment. Insofar as it appears that the change processes begin well before treatment entry, it may be that treatment is more a result of change rather than a cause of it. Even if that were the case, though, treatment could still have important effects such as prevention of relapse, or more rapid or profound or more gratifying change.

Historically, research on professional psychosocial interventions focused first on development of theoretical frameworks to explain change and to direct intervention efforts. Examples of such frameworks include cognitive-behavioral, twelve-step, and motivational enhancement. Subsequent research in this area included studies to refine

the internal validity of studies of these frameworks using therapy manuals, training, and monitoring; development and use of well-validated and reliable instruments; and improved research designs such as randomized controlled trials. The results were unexpected: treatments with very different conceptual frameworks and intervention techniques have approximately equivalent (and reasonably good) outcomes (e.g., abstinence or significantly decreased drinking and consequences). Furthermore, relatively brief, non-intensive treatments yield outcomes as good as more intensive treatments. These results suggest that non-specific factors such as a decision to seek help, installation of hope, empathy and the therapeutic alliance may be more important that specific factors hypothesized by treatment models. An alternative explanation is that the mechanisms are specific to each technique but they lead to a common outcome. One reason that the two alternatives have not been differentiated is that research to date has primarily focused on simple efficacy comparisons, and therefore has been silent on the question of what the mediators and moderators of change in these treatments actually are.

E. Treatment: Medications Development

While for many years, alcoholism treatment approaches relied almost exclusively on behavioral therapy, efforts to develop medications for alcohol use disorders have expanded rapidly in recent years. Three agents -- disulfiram, naltrexone, and acamprosate -- are now approved for use in the United States and many other countries. As is the case with medications for other chronic diseases, these medications have been found to be highly effective with some patients but others have failed to respond to them. New medications, providing effective therapy to a broader spectrum of alcoholic individuals, would be of value for the treatment of alcohol dependence. Research findings revealing that drinking and alcohol-seeking behavior are influenced by multiple neurotransmitter systems, neuromodulators, hormones, and intracellular networks provides evidence that there are a number of potential target sites for which new pharmaceuticals may be developed. Potential target sites include neurotransmitter systems related to opioids, serotonin, dopamine, glutamate, gamma-aminobutyric acid (GABA), cannabinoids, the hypothalamic-pituitary-adrenal (HPA) axis, adenosine, neuropeptide systems (for example, neuropeptide Y, corticotrophin releasing factor), signal transduction pathways (such as, protein kinase A and protein kinase C); and gene transcription factors (delta fos B and cAMP response element-binding protein [CREB]). Indeed, many such agents are under test as shown in Table V-3. Among these agents several promising compounds are currently being considered as candidates (baclofen, rimonabant, and memantine) for evaluation to determine their safety and efficacy in the treatment of alcohol use disorders and it is likely that additional agents will be identified as medications development efforts for alcoholism proceed.

Table V-3. NIAAA Medication Development Lead Compounds

Medication under development	Mechanism	Pre Cln	Ph1	Ph2	Ph3
Naltrexone depot formulation (Vivitrex®) Alkermes)	Opiate antagonist				**X**
Topiramate (Topamax™ Ortho-McNeil)	Facilitates GABA and inhibits glutamate activities			**X**	**X**

Gabapentin (Neurontin™ Pfizer)	Facilitates GABA and inhibits glutamate activities			**X**	
Ondansetron(Zofran™ GSK)	5-HT_3 antagonist			**X**	
Baclofen (FDA approved)	$GABA_B$ agonist			**X**	
Aripiprazole	Dopamine partial agonist			**X**	
rimonabant (Acomplia™ Sanofi-Synthelabo)	Cannabinoid CB_1 antagonist		**X**	**X**	
Adenosine A_2 antagonists	Adenosine A_2 antagonists	**X**			
Memantine (Namenda ™ Forest Laboratories)	glutamate NMDA antagonist		**X**		
CRF_1 antagonists	CRF_1 antagonists		**X**		
CRF_2 agonists	CRF_2 agonists	**X**			
NPY agonists/antagonists	NPY agonists/antagonists	**X**			
Kudzu extract	Unknown		**X**		
2-Methyl-6-(phenylethynyl)-pyridine (MPEP)	mGluR5 antagonist	**X**			
Diphenylureido compound, DCUKA	glutamate NMDA antagonist and a voltage-sensitive sodium channel blocker	**X**			

The development of new medications for alcoholism is greatly aided through the use of animal models for the screening of new agents that can alter attributes associated with alcohol dependence. Several laboratory paradigms which model facets of alcoholism are now used to study the behavioral effects of alcohol in mice, rats and monkeys. These include:

- Models that involve self-administration of large amounts of alcohol sufficient to produce tolerance, withdrawal and high blood ethanol levels (i.e., > 100 mg/dl). These behaviors are found in animals predisposed to prefer alcohol solutions (e.g., selectively bred strains), or after induction periods under certain conditions (e.g., dependence-induced drinking).

- Animals that are motivated to procure alcohol when no longer available, or in the face of impediments or negative consequences. Drinking attributes can be evaluated for these models using operant self-administration paradigms. These animals model obsessive-compulsive attributes of human alcohol dependence characterized by craving, and drinking despite adverse consequences.

- Cycles of remission and relapse to drinking can be modeled using alcohol deprivation paradigms.

- Environmental events triggering an episode of alcohol seeking following a remission period can be modeled in a reinstatement paradigm.

Therefore, while it is now possible to model some attributes of dependence, craving, lapse, and relapse using a variety of current animal laboratory paradigms, new models that more closely model the endophenotypes and intermediate phenotypes (for definitions see Table I-10) involved in the development and expression of alcoholism would greatly benefit medication development efforts. For example, the endophenotype of neural disinhibition may be modeled in different animal models and prove useful as a tool for medication development research.

Another aid in the search for new medications is through human laboratory testing. Testing of model therapeutics, in a human laboratory environment with a relatively small subject population carefully selected for their targeted drinking behavior can provide a significant savings in the time and cost associated with clinical trials for the development of new medications. These efforts are undertaken after animal pre-clinical screening. Currently, there is no consensus on the best way to evaluate drugs to treat alcoholism in the human laboratory environment, although two models have been used: alcohol self-administration and relief from the symptoms of alcohol protracted abstinence. The continued study of these laboratory animal models, and the development of new models is timely and required for rapid progress to be made in the screening of targeted compounds shown to offer promise from animal studies.

The identification of new biomarkers to provide an early indication of treatment success would be a great asset in medications development. During the past years, efforts have been made to develop and characterize new as well as traditional biomarkers of alcohol consumption and alcohol-induced tissue injury. Traditional biomarkers of alcohol consumption include gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and corpuscular volume (MCV). Newer markers include carbohydrate-deficient transferrin (CDT), 5-hydroxytryptophol (5-HTOL), a serotonin metabolite, and ethyl glucuronide (EtG), a metabolite of alcohol.

In addition to biomarkers of alcohol consumption, biomarkers of alcohol-induced tissue injury are also of importance. Such potential markers for alcoholic liver disease include alpha-smooth muscle actin (SMA), fibronectin, collagen type I, serum hyaluronate, matrix metalloproteinase (MMP)-2, and MMP-9.

However, current biomarkers, for the most part, lack specificity or sensitivity, or have a very short half-life. Due to the limitations of these biomarkers, it is vital to discover new biomarkers that are unique to alcohol consumption and/or alcohol-related diseases. Recent advances in high-throughput technologies for proteomics, genomics,

and metabolomics have been successfully used for studying complex biological problems and show promise for the identification of individual biomarkers and unique signatures. These high-throughput technologies have created new exciting opportunities for discovering and developing novel biomarkers that may be useful for alcohol-use disorders.

Another important direction for medications development research lies in pharmacogenetic research, that is, the identification of genetic subtypes of alcohol dependence that respond to specific pharmacologic agents. Research in recent years has discovered specific genetic variants that may contribute to the risk for alcoholism, and which may define specific sub-sets of alcohol dependent individuals who respond to specific therapeutic agent. Among the genetic variants are the $GABA_A$ receptor genes *GABRA2* and *GABRG3* that have recently been associated with alcoholism. Other promising sites include the short versus the long allele of the serotonin transporter, the presence or absence of the A1 allele of the dopamine D_2 receptor gene, catechol-O-methyltransferase (COMT) Val158Met allele, and the NPY gene variant Leu7Pro. Also included here, as discussed in the context of protection versus susceptibility for alcoholism, are the polymorphisms in the alcohol dehydrogenase gene *ADH1B* and the aldehyde dehydrogenase gene *ALDH2.* Consideration of an individual patient's unique genetic profile and phenotypic characteristics may help in the future for selecting the most effective anti-alcohol medication. Although research is in early stages, some advances have been made. A polymorphism in the gene that codes the opioid *mu* receptor (A118G, which causes an Asn40Asp substitution in the protein) has recently been associated with the response to naltrexone in alcohol dependent patients and to a family history of alcoholism, alcohol intoxication, and alcohol-induced stimulation and sedation. In a preliminary study, alcoholic patients treated with the drug olanzapine who possess the dopamine *DRD4 L* allele (7 or longer repeat allele of the tandem repeats [VNTR]) experienced reduced craving for alcohol, while olanzapine did not reduce craving in those with the *DRD4 S* allele.

Progress has also been made with respect to defining new medication targets for organ pathologies. In particular, cytokines, reactive oxygen species (ROS), and other primary factors in the onset and progression of alcoholic liver disease may prove fruitful as medication targets. For example, it has been found that the severity of alcohol-induced liver injury in rats could be reduced through the administration of antibodies against tumor necrosis factor α (TNF-α), a molecule that promotes inflammation. Antioxidants such as Vitamin E, glutathione, or its methyl donor, S-adenosyl-L-methionine (SAMe) also have shown potential for treating alcoholic liver disease. These compounds can quickly inactivate ROS, by-products of alcohol metabolism that can damage the liver. Research suggests that cannabinoid CB_1 antagonists and CB_2 agonists may be a potential therapeutic target for alcohol treatment given their close association with the reward centers of the brain (nucleus accumbens) and their modification by ethanol intake in animal studies. Furthermore, metformin, an insulin-sensitizing agent, also warrants further study as a potential medication for alcoholic liver disease.

F. Opportunities

Metabolism and Organ Injury

- The mechanisms by which alcohol may elicit altered metabolic and physiological states in disease development common to multiple organs within the body can be more comprehensively pursued including the exploration of how alcohol and its metabolic intermediates, such as reactive aldehydes, ROS and alterations in the redox state of the cell change following alcohol consumption. Research on the consequences of such changes may be approached by examining the direct and indirect actions of alcohol in altering transcription factors, cytokines and other agents altering communication networks within the body.

- Continued research on the effects of alcohol at low and moderate dose levels may be feasibly approached to further uncover the mechanism underlying both pathologic and potential beneficial outcomes of these levels of alcohol exposure. Longitudinal research may be entered into collaboratively with other institutes of the NIH in the overall study of a range of alcohol and non-alcohol related diseases.

- Investigate how alcohol influences the disease course of various pathogens, such as Hepatitis C and Hepatitis B.

- Examine whether alcohol's effect on HIV infection and AIDS progression varies with age of infection

- Identify the alcohol-related factors associated with increased HIV infectivity, such as viral shedding, the alteration of HIV variants through such processes as epigenetics, and the potential effect of alcohol on metabolism of anti-HIV medications.

- Identify how alcohol contributes to organ and tissue damage in HIV-infected individuals.

- Determine the implications of alcohol and AIDS basic science discoveries for prevention and treatment research.

Treatment and Behavioral Change

- Behavioral research should be further pursued to identify biological factors and contextual social factors that contribute in the decisional process to change drinking behavior involved in the transitional process out of alcohol dependence, and the factors that are the underpinning of sustained recovery among those individuals who succeed in both the presence and absence of professional treatment. Measures reflective of these factors might include those of implicit cognition, hedonics, arousal, or emotion, and these measures might be suggestive of the decisional process to inflect change or the sustained recovery from alcoholism. Naturalistic, qualitative and longitudinal studies can identify factors influencing natural history and disease course, in order to inform more explanatory studies.

- Increase understanding of the role of social context in promoting or retarding positive change in drinking behavior. Included within the context of social factors are marital or other partners, friendship and kin networks, employment environments, legal and economic environment (availability and price of alcoholic beverages, proximity to outlets, DWI laws), religious groups, mutual help groups, and similar activities. This research needs to be approached over a time dimension to aid in defining the mediators and moderators underlying successful transitions and include an identification of the time course of the various stages of change.

- Develop animal models that more closely reflect the human endo- and intermediate phenotype underlying the clinical syndrome phenotype.

- Apply new technologies in neuroscience research to further understand how acute as well as chronic alcohol use affects neural circuits (rather than gross morphological brain areas), and how neural circuits are modified by treatment and recovery. In terms of neural circuits, use objective measures of brain function such as EEG and specific brain imaging techniques (e.g., diffusion tensor imaging) to identify potential intermediate phenotypes, or endophenotypes (see Table I-10), associated with alcoholism and the effects of treatment. Furthermore, measures of implicit cognition, and neurofunctional changes associated with cognitive/emotional deficits in alcoholic subtypes and recovering alcoholics would be a novel focus. This research could best be accomplished by transdisciplinary collaborations among behavior, social and neuroscience researchers.

- Apply insights and methods -- such as model development using sophisticated statistical techniques -- developed in neuroscience, immunology, oncology, sociology, genomics, metabolomics and other fields to study change in drinking behavior.

Medications Development

Increase the number of medications available for the treatment of alcoholism to reach a broader spectrum of individuals with alcoholism. To accomplish this goal, the following initiatives are currently timely and feasible:

- Identify new target sites in the brain for which lead compounds could be developed. Identification of new target sites requires an expansion of basic neuroscience research to uncover the neurocircuits underlying relevant behaviors including: biological reward; alcohol-seeking behavior, protracted withdrawal symptoms, craving, and the psychological and social dynamic attributes of drinking. The NIH Roadmap Molecular Library which has been established provides a repository for many potential test compounds to accelerate progress in identifying both the molecular sites and lead compounds.

- To facilitate the testing of lead compounds, develop animal models that more closely reflect the human endo- and intermediate phenotype underlying the clinical syndrome phenotype. It is anticipated that multiple models will be

required as no single animal model can fully model the clinical syndrome phenotype of human alcoholism. Given the diversity of models, pharmaceuticals targeted to different aspects of alcohol dependence may be pursued and effective pharmacotherapy for some individuals may require multiple therapeutic agents. Positive outcome from evaluations of test compounds with animal laboratory paradigms will guide decisions about whether lengthier, more expensive, clinical tests in human alcoholics are warranted.

- Develop human laboratory paradigms modeling surrogate outcomes for alcoholism treatment. This requires an understanding of expressed behavioral or physiological traits (endophenotypes and intermediate phenotypes) associated with the risk for, or expression of alcoholism. Potential new markers include cue sensitivity, neural inhibition, and other electrophysiological indicators to add to those already available.

- Expand efforts in pharmacogenetic research to identify genotypic and phenotypic characteristics of patients that predict efficacy and safety of different medications. Such research will help delineate alcohol dependence subtypes and offers the clinician the potential to prescribe medication regimens tailored to the individual. In recognition that pharmacogenetic variants do exist, it is important to formulate methodological and statistical strategies to select the most appropriate outcome measures for detecting moderate-sized effects in alcohol pharmacotherapy trials.

- Identify and develop novel biomarkers and other surrogate endpoints to measure success objectively in pharmacotherapy trials. As well, apply the technology of the non-invasive, continuous monitoring biosensor for the measurement of alcohol, and other appropriate analytes, to monitoring of pharmaco- and other treatment effectiveness and in particular, to study dynamics of relapse.

- Continue research targeted to the prevention and treatment of alcohol-related organ pathologies involving anti-oxidant agents, and cannabinoid related agents.

- Develop collaborative networks among government, academia, and industry in order to overcome the many challenges in development of medications to treat alcohol problems. Establishing these partnerships will allow for a more comprehensive effort to discover and develop safe, effective medications, and for the application of the resources of the NIH Roadmap such as molecular libraries, and infrastructures for clinical protocol testing.

G. Outreach

- NIAAA has developed working relationships with many outside organizations with missions and goals that extend the ability to move research results to practice and to the public. Jointly, the NIAAA seeks to assure informed and

research based policy and program decisions by these organizations and to provide support to assist in the distribution of alcohol research knowledge. The NIAAA collaborates with these organizations by providing symposia, workshops and meetings in which alcohol researchers or staff present relevant study results.

- A Memorandum of Understanding (MOU) between the NIAAA Division of Intramural and Clinical and Biological Research and the School of Medicine at Howard University will provide for the co-mentoring of pre-doctoral students including participation in research, seminars, examinations and short-term rotations. This partnership provides NIAAA opportunities to: explore mechanisms and develop hypotheses that may alleviate health disparities in alcohol related problems; provide education and information to the community and to health care providers which will aid in the prevention and treatment of alcoholism and alcohol abuse; increase the participation of minorities in research studies at NIAAA and Howard University.

- Use state-of-the-art communication strategies and techniques to increase awareness of critical alcohol and health messages, including that: research-based treatments improve the health and well-being of individuals with alcohol problems; research promises to further elucidate mechanisms of alcohol damage and lead to targeted interventions.

CHAPTER VI. Senior Adult

A. Background

Aging is associated with a variety of changes that place senior adults at special risk for alcohol-related health problems. As people live longer, the absolute number of senior adults who continue to drink as they age will increase. Since the percentage of aging individuals in the general population is steadily increasing, the number of senior adults with problem drinking habits will become a national healthcare issue. Senior adults are known to differ in their physiological and behavioral responses to alcohol in a variety of social contexts, and their ability to respond to alcohol tolerance is greatly altered during the senior years. Drinking can aggravate a variety of pathological conditions in the senior adult including stroke, hypertension, neurodegeneration, memory loss, mood disorders, and cognitive or emotional dysfunction. Notwithstanding the obvious problems associated with diagnosing problem drinking in the senior adult population, including the similarities in alcohol-related and age-related manifestations, the results of studies may be influenced by the location of the subjects at the time of measurement (e.g., nursing home or assisted care facility, independent living in retirement community, hospital, primary care setting).

B. Epidemiology

Although senior adults drink less than other adults, their pattern of alcohol consumption has changed over time; more recent birth cohorts of seniors tend to drink more than less recent birth cohorts, which represents generational shifts in attitudes about alcohol consumption over time. Therefore, more aging individuals will be drinking more and the health related issues resulting from this fact will change the need for better surveillance of the problems faced by the future generations.

Table VI-1. Percentage of U.S. Adults 18 and Over with Past-year Alcohol Abuse or Dependence and Percentage of Those with Past-year Abuse or Dependence Who Received Alcohol Treatment, by Type of Treatment

	Past-year disorder		Type of treatment			
Age group	Abuse	Dependence	Any treatment	12-Step only	Other only	12-Step and other
60+	1.4 (0.1)	0.5 (0.1)	3.4 (1.3)	1.9 (1.1)	0.8 (0.6)	0.6 (0.4)

Source: Adapted from Table I-8 in the overview.

As shown in the table above (Table VI-1), only 0.5 percent of individuals over 60 met criteria for a diagnosis of alcohol dependence during the previous year. Only 1.4 percent met a diagnosis of alcohol abuse. Despite this, only 3.4 percent of those meeting a diagnosis of either alcohol dependence or alcohol abuse had, at some point in their lives, treatment for their alcohol-use disorder.

Longitudinal studies indicate the majority of those individuals who drink heavily as seniors were also heavy consumers over the course of their adult years before entering the senior adult years. Consumption of alcohol has declined more slowly among the more recent cohorts of older individuals as subsequent generations of senior

adults are influenced by generational attitudes towards drinking. This has significant implications for healthcare of future senior adult populations. An important distinction is made between individuals with an early onset versus late onset of problem drinking: those with a late onset (the majority are female) have a better chance at recovery and fewer alcohol-health related problems than those with an early onset of problem drinking, although little research on this specific topic has been performed. However, alcohol misuse in the senior adult population remains an important public health issue since older individuals are more likely to have additional health problems that may confound accurate diagnoses of wholly organic versus wholly alcohol problems.

One of the major issues with respect to estimating the prevalence of alcohol abuse in senior adults involves survey location, e.g., estimates are lowest from community-based surveys (those that sample from senior adults living in independent settings), increased from health care settings (hospital admissions from emergency room and psychiatric wards), and the highest estimates were derived from studies within nursing and critical care facilities, and the diagnostic criteria with which senior adults are compared for the purpose of diagnosis (many of the criteria are not relevant for the senior adult with drinking problems).

C. Etiology

The etiology of problem drinking by older persons is not well studied. Obviously, senior adults differ from other adults in physiology, biology and social aspects, all of which may contribute to higher alcohol consumption on average in the senior adults. In terms of biological effects, senior adults have a smaller body mass and lower water content than other adults, thus the blood alcohol concentration attained for like-amounts of alcohol consumed will differ between these groups of individuals independent of their inherent metabolism. Senior adults are more likely to have intrinsic problems with health issues related to blood pressure, sleep patterns and bone metabolism, for example, which may prompt an increase in alcohol consumption to offset the perceived effects of such medical conditions. Senior adults take more medications than other adults, therefore causing a potential reduction in the effectiveness of medications taken to alleviate specific medical conditions.

There are various social factors that may result in increased alcohol consumption in senior adults, such as loss of a spouse, lack of or reduced family support, and the availability of disposable income to engage in drinking. Furthermore, the period of retirement may be a risk factor in the development of increased alcohol consumption since senior adults have more unstructured free time and no longer have job-related ramifications of heavy alcohol consumption. Individuals in any age range may misinterpret the information regarding the benefits of alcohol consumption on general health (including misinterpretation of amount and frequency that may produce the benefit). For senior adults, the consequences of inappropriately weighing the relative risk versus benefit of alcohol consumption for their age group may have particular negative consequences with regard to their personal medical conditions.

D. Treatment and Prevention

There is some evidence that senior adults will respond positively to treatments especially if they are treated within groups consisting of similar-aged individuals. Senior adults with late onset problem drinking (more typical of female than male) and shorter

history of problem drinking tend to respond more positively to treatment efforts than those with early onset problem drinking. The most efficacious therapies seem to involve cognitive-behavioral therapy and group and family therapy, which tend to involve familial support mechanisms that may have been an exacerbating factor for the increase in late-life alcohol abuse. There is some indication that medications developed to promote abstinence may not work as well in senior adults given that the mechanism of benefit may be altered due to age-related issues (more so than to alcohol-related issues), although this area is not well studied in the clinical population.

Similarly, based on the current literature, the most beneficial prevention of senior adult alcohol abuse is education, since some reports indicate that lack of knowledge about alcohol abuse rather than a disregard for the information was at the root of some problems associated with relapse in senior adult problem drinkers. Since there is no definitive phenotype for the senior adult problem drinker, the development of current prevention efforts must be geared towards generalized personality or situational characteristics that have led to problem drinking in like-age groups of individuals.

E. Opportunities

Although the fundamental processes responsible for normal chronological aging clearly can influence individuals' responses to alcohol, the basic biological mechanisms underlying this relationship have remained largely unexplored. Recent studies have yielded exciting new information about how chronological aging affects brain function, cardiovascular function, endocrine function, and immune function. Likewise, there has been dramatic progress in alcohol research from genetic to behavorial and cognitive levels. These advances, together with recently developed technologies and experimental models, provide important new opportunities to examine how mechanisms affected by alcohol exposure and aging interact with one another. Some of these mechanisms may mediate altered physiological functions in different tissues, while others may participate in degenerative processes leading to tissue damage.

- Current understanding the metabolic changes that occur with the progression of age is very limited. Technologies introduced in the last decade that permit a more detailed understanding of alcohol metabolic pharmacokinetics including alcohol clamping, and the examination of differential expression of genetic (genomic) protein (proteomic) and metabolic (metabolomic) profiles that have either been recently developed, or that will emerge from initiatives within the NIH Roadmap, can provide important information pertinent to individuals across the senior adult age ranges. These same technologies can be applied to important metabolic consequences associated with the range of pharmaceuticals taken by individuals in the senior age range given the common use of medications in the age group.

- As efforts continue in the development of new medications for the treatment of alcohol dependence, a focus on the effectiveness of these emerging pharmaceuticals in the senior adult population, given the differences in physiology and potential interactions with other medications taken by this group will be an important adjunct to such research.

- The changing demographics in the age of the U.S. population may translate into significant changes in the contexts of alcohol use in the senior adult

population, as well as, the social consequences of that use. The continued monitoring of these changes will be important given the impact that alcohol may have on this population. Longitudinal assessments of the use, impact, and consequences of alcohol use, coupled into other longitudinal assessments jointly undertaken by multiple institutes of the NIH, will offer a cost effective approach for obtaining this important information. Such efforts also provide a cost effective means to determine the relationship of alcohol in the development of such disorders as Alzheimer's disease, Type II diabetes, and others that ncrease with age.

- Animal models of alcohol abuse and aging can be used to examine specific contributions of alcohol to aging organ pathology (e.g., brain, liver, heart).

F. Outreach

- Working with the NIA, Association for the Advancement of Retired Persons (AARP), and Medicare, NIAAA will increase the transfer of information to practice for seniors through publications and assuring that health care providers have appropriate information. Co-sponsorship of meetings and conferences will be used to foster working relationships.